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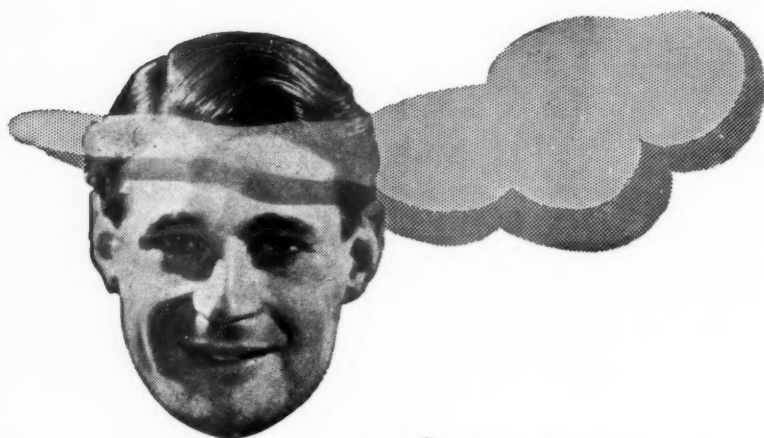
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## Clinical Section

President—JAMES L. LIVINGSTONE, M.D., F.R.C.P.

[October 8, 1954]

### Three Cases of Haemolytic Anæmia.—J. F. HORLEY, M.B.

*Case 1.*—B. M., male, aged 18.

First admitted 10.10.50 for dyspnoea and throbbing headache present for one month. He was pale and slightly icteric with a palpable spleen.

*Investigations.*—Bone-marrow hyperactive but otherwise normal; direct Race-Coombs test strongly positive; urobilinogen present in the urine; hæmoglobin estimations and reticulocyte counts shown in Fig. 1. Blood transfusion was given without permanent benefit and after one month's observation, splenectomy was performed. Rapid improvement ensued and the blood reverted to normal after four months, except that the direct Race-Coombs test was still positive.

He remained well until January 1952 when, nine days after an attack of tonsillitis and cervical adenitis, he became slightly icteric and was readmitted. Investigations showed reactivation of hæmolytic (Fig. 2). He was given ACTH 200 mg. daily for two months.

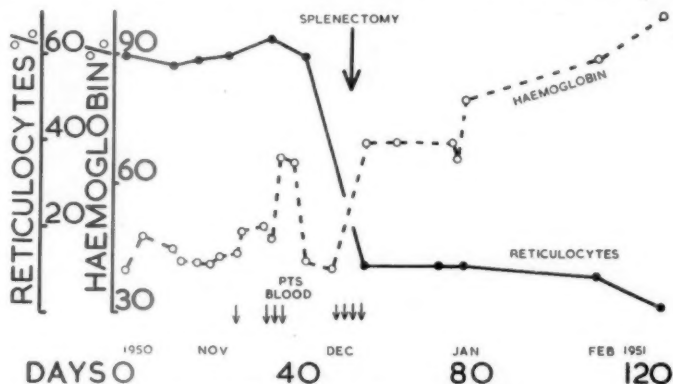


FIG. 1.—Case 1. First episode. Response to splenectomy.

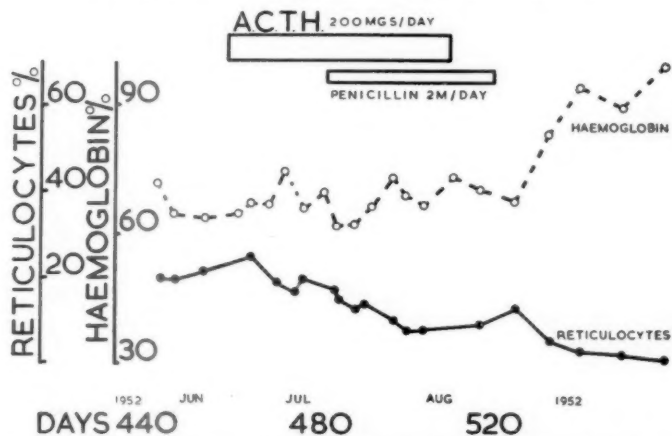


FIG. 2.—Case 1. Second episode. ? Doubtful response to ACTH and penicillin.

After one month of ACTH an evening pyrexia of 100–101° F. developed, accompanied by chest pain and a pulmonary systolic murmur; chest X-ray was normal and blood culture negative. He was given penicillin 500,000 units six-hourly for one month. He improved steadily and was discharged fourteen weeks after his second admission.

At the present time he is working and in good health. His blood picture is normal, including a negative direct Race-Coombs test.

**Case II.**—Mrs. T., aged 72.

First admitted 26.6.53 with increasing dyspnoea and weakness present for two weeks. She was pale, slightly icteric with a palpable spleen.

**Investigations.**—Bone-marrow hyperactive but otherwise normal; direct Race-Coombs test strongly positive; haemoglobin estimations and reticulocyte counts shown in Fig. 3. The Donath-Landsteiner reaction was negative, cold agglutinins present to a titre only of 1 in 4, red cell fragility slightly increased and spherocytes present in the blood film. Transfusion was given twice without permanent benefit. From July 28, 1953 onwards cortisone was given in dosages shown in Figs. 3 and 4; striking subjective and objective improvement occurred. Two weeks after cortisone was commenced a subcutaneous abscess developed overlying the sacrum; this was drained and healed normally.

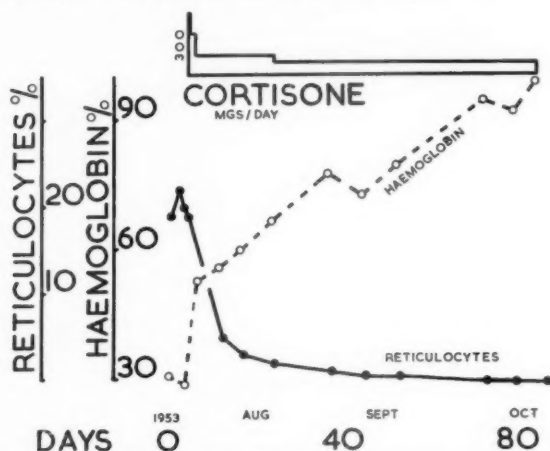


FIG. 3.—Case II. First episode. Clear cut response to cortisone.

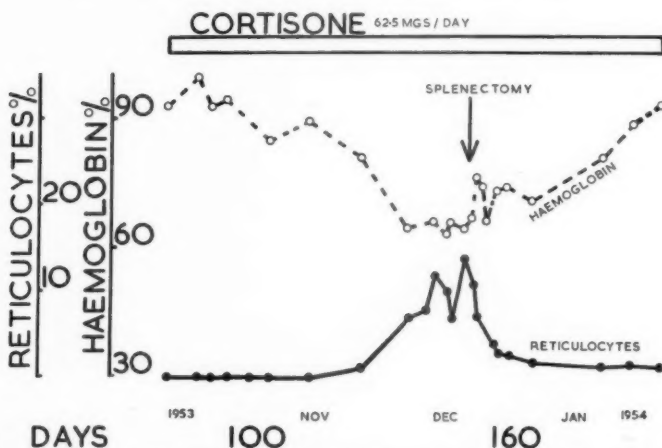


FIG. 4.—Case II. Second episode. Relapse under cortisone and response to splenectomy.

Progress was maintained until November 1953 when as shown in Fig. 4 the blood count deteriorated. Splenectomy was performed on 22.12.53; post-operatively she made steady progress until February 1954 when she developed thrombosis of the deep veins of the left leg. Two weeks later she suffered two pulmonary emboli and was treated with anticoagulant therapy. In July 1954 anticoagulants and cortisone were both discontinued (Fig. 5).

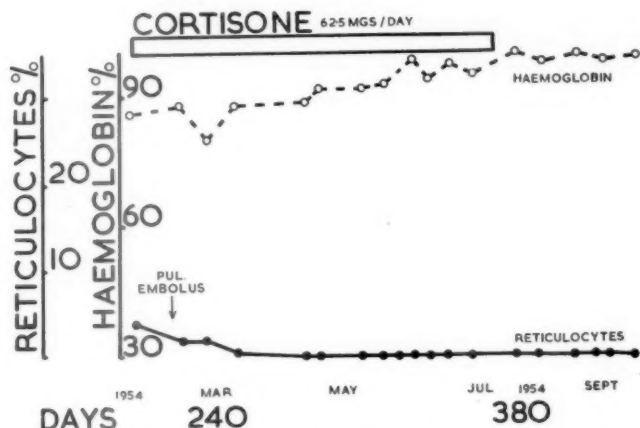


FIG. 5.—Case II. Progress maintained. Cortisone discontinued.

At present she is symptomless and feels well. The blood picture is normal except that the direct Race-Coombs test remains strongly positive.

*Case III.*—Mrs. M., aged 78.

In October 1952 she complained of pallor, jaundice and dyspnoea. She was treated by her own doctor without pathological investigation and improved subjectively. In June 1953 she complained of abdominal swelling which proved to be an enlarged spleen.

*Investigations.*—Bone-marrow hyperactive but otherwise normal; serum bilirubin 3 mg./100 ml.; direct Race-Coombs test strongly positive; Donath-Landsteiner reaction

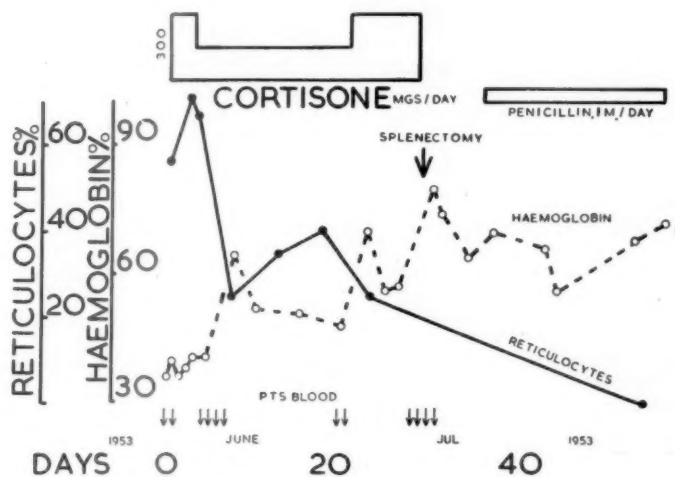


FIG. 6.—Case III. First episode. No response to cortisone.

negative; cold agglutinins present to a titre of only 1 in 32; red cell fragility slightly increased and spherocytes present in the blood film. Haemoglobin estimations and reticulocyte counts shown in Fig. 6. She was treated with cortisone and blood transfusion but showed no clear-cut response and splenectomy was performed one month after admission; a post-operative pyrexia accompanied by a small pulmonary embolus was treated with two weeks' penicillin 250,000 units six-hourly.

She remained well until May 1954 when she developed jaundice and dyspnoea. Cortisone 100 mg. daily was given with some benefit. In June 1954 she complained of a choking sensation in the chest and loss of voice; chest X-ray revealed a shadow in the upper mediastinum which in retrospect could be seen in chest X-rays as early as May 1953. A course of deep X-ray therapy was given with subjective relief. Withdrawal of cortisone was attempted but she became more anæmic (Fig. 7) and 100 mg. daily was resumed.

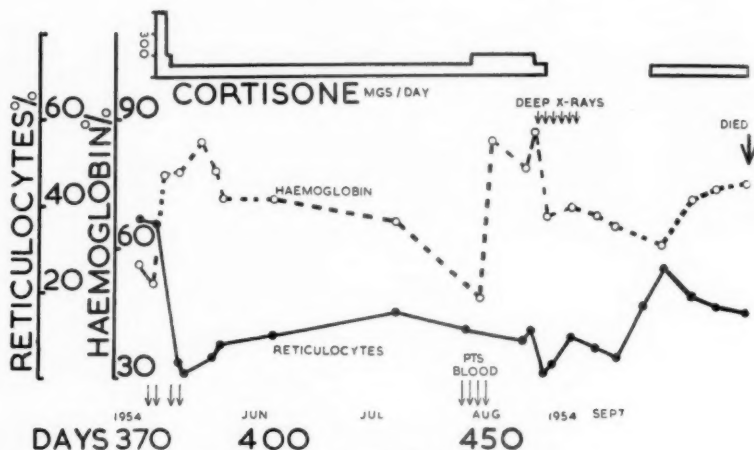


FIG. 7.—Case III. Second episode.

Since this case was shown the patient has died. Post-mortem examination revealed a lymphosarcoma affecting the mediastinal and para-aortic glands. The immediate cause of death was pericarditis due to direct extension of the mediastinal tumour into the pericardium.

*Comment.*—The first 2 cases are examples of idiopathic hæmolytic anæmia, the third was associated with lymphosarcoma.

The response to cortisone has varied: in Case II it was immediate and striking but relapse nevertheless occurred while on maintenance dosage. In Case I there was only slight response to ACTH; in Case III cortisone, while not entirely successful, seemed to check hæmolysis since anæmia became more pronounced when it was withdrawn. Another idiopathic case seen recently was successfully treated with cortisone, while a case of hæmolytic anæmia secondary to carcinoma of the stomach showed no response at all.

Benefit from splenectomy was immediate in Cases I and II, but was less clear cut in Case III. In a case of reticulosarcoma seen recently with a severe hæmolytic anæmia (Hb 35%) immediate and lasting alleviation of anæmia was produced by splenectomy until death fourteen months later from cachexia.

The possible relationship between hæmolysis and infection is interesting and has been reported by Best *et al.* (1951). In Case I the second episode occurred following tonsillitis and recovery was coincident with penicillin therapy (Fig. 2). In Case II recovery also seemed to be influenced by penicillin and, in view of this, empirical antibiotic therapy may be justified in similar cases.

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BEST, W. R., LIMARZI, L. R., and PONCHER, N. G. (1951) *J. Amer. med. Ass.*, 147, 827.

**Cruveilhier-Baumgarten Anomaly.**—ELEANOR M. R. TILL, M.B., and P. KYNASTON THOMAS, M.B. (for D. G. FERRIMAN, D.M.).

The patient was presented to the Section in December 1953 (*Proceedings*, 1954, 47, 257). C. H., male, aged 44.

Admitted to the North Middlesex Hospital on 13.10.53 following hæmatemesis and melena. Examination revealed a venous swelling superficial to the xiphoid process over which there was a continuous thrill and murmur, and splenomegaly. The liver was not enlarged. Barium swallow showed oesophageal varices. Diagnosis: portal hypertension, aetiology uncertain.

Lieno-renal anastomosis was performed but unfortunately thrombosis occurred in the splenic, portal and umbilical veins. The patient died on 20.4.54.



FIG. 1.

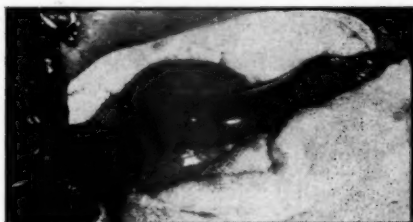


FIG. 2.

Figs. 1 and 2.—Appearances of umbilical vein at laparotomy.

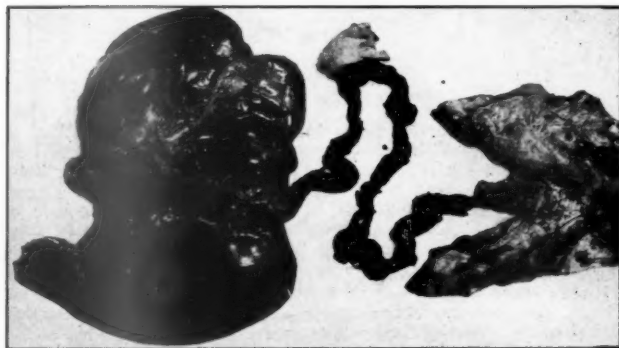


FIG. 3.—Dissection displaying connexions of umbilical vein.

**Post-mortem examination (Figs. 1-4).**—The liver weighed 1,100 grams, its surface was smooth and histologically there was slight monolobular cirrhosis. The splenic and portal veins were dilated and contained recent ante-mortem thrombus. A large tortuous vein (see Figs. 1 and 2) lying in the free border of the falciform ligament, identified as a persistent left umbilical vein, linked the left branch of the portal vein with a more superficial vein in the falciform ligament; this vein terminated in a varicosity overlying the xiphoid process (Fig. 3) which was connected with the internal mammary veins. These were of normal diameter. The direction of blood flow had been demonstrated at operation to be from the portal to the systemic veins and the murmur had been localized to the venous swelling over the xiphoid process; no murmur was heard over the liver or elsewhere in the abdomen.

The presence of oesophageal varices was confirmed. The biliary system and the hepatic arteries and veins were normal. X-ray of the liver after injection of barium suspension into the portal and hepatic veins revealed no abnormality.

6 cases of Cruveilhier-Baumgarten anomaly have been described previously and the condition has recently been reviewed by Jahnke *et al.* (1954). The anomaly consists of portal hypertension associated with a patent umbilical vein and unaccompanied by

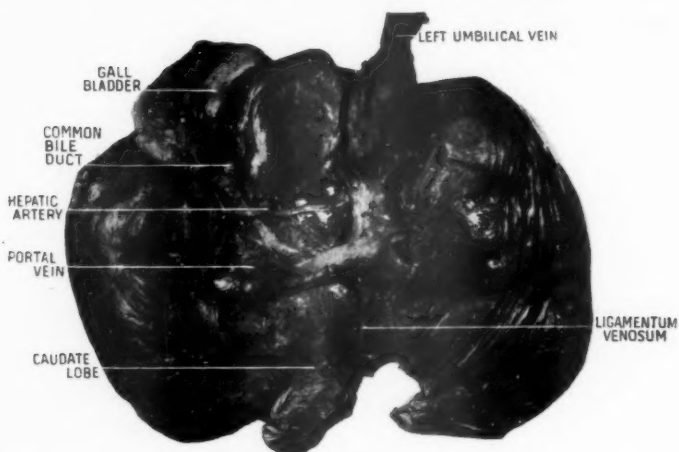


FIG. 4.—Photograph of inferior surface of liver.

significant hepatic cirrhosis. The condition presumably involves the appearance of portal hypertension at birth resulting in the persistence of the umbilical vein and the development of anastomoses between it and the epigastric or internal mammary veins. The nature of the resistance to blood flow through the liver remains obscure.

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JAHNKE, E. J., PALMER, E. D., and BRICK, I. B. (1954) *Ann. Surg.*, **140**, 44.

#### Hyperinsulinism Treated by Partial Pancreatectomy.—A. KAHAN, M.D., M.R.C.P.Ed., D.C.H.

C. N., male, aged 38.

This patient was first seen in November 1953 when his main complaints were that for some years he had felt tired and listless, and that he had been subject to attacks of "light headedness". The attacks sometimes came on half to one hour after a meal, but he was not very certain about this. More general symptoms of inability to concentrate, difficulty in remembering things, and a sensation of unreality, were certainly not related to taking food. He lacked energy, and became tremulous and sweated on attempted exertion. It was difficult to determine the onset of these symptoms because from the age of 7 years he had been subject to *petit mal* and had taken phenobarbitone for the past twenty years.

*On examination.*—No organic cause for his symptoms was discovered. The fasting blood sugar was 75 mg. %. Further blood-sugar studies were as follows:

(a) A standard "glucose tolerance curve". After 50 grams glucose the blood sugar rose to 95 mg. %, and then fell to 40 mg. %. The patient did not become unconscious but was reported as "rolling about like a drunk" (Fig. 1).

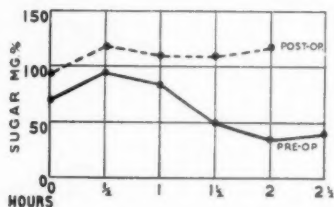


FIG. 1.—Comparison of blood-sugar curves before and after operation.

(b) Another tolerance test, starting with oral glucose and followed by a high protein meal in four hours, showed a similar early fall in blood sugar.

(c) 50 grams glucose given by intravenous injection caused an initial rise to 150 mg.%, followed by a fall to 66 mg. %.

(d) A continuous intravenous drip of 40 grams glucose per hour, given in 15% solution, caused a rise to 216 mg. % in an hour, followed by a fall in blood sugar to 86 mg. % (Fig. 2). The test was continued for four hours. This was regarded as a crucial test for hyperinsulinism as it is considered that this rate of administration should result in hyperglycemia and glycosuria within two hours.

The curve is contrasted with that of another patient, in whose case a single glucose tolerance was suggestive of hyperinsulinism, but the continuous glucose resulted in hyperglycemia at one, two, and three hours after the drip was commenced (Fig. 2).

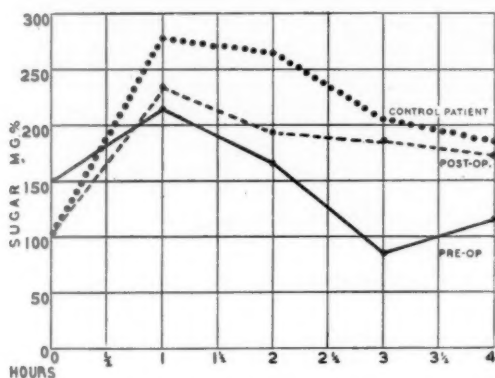


FIG. 2.—Comparison with a normal curve during intravenous glucose drip before and after operation.

In addition to these studies, investigations included X-ray of skull (normal pituitary fossa), lumbar puncture (normal C.S.F. and negative W.R.) and EEG. The last was of especial interest in view of the previous diagnosis and treatment as a case of *petit mal*, and also because many of the recorded cases of hyperinsulinism have presented with attacks simulating epilepsy. Indeed, an EEG with suppression of normal alpha rhythm is regarded by some authorities as an important diagnostic feature of hyperinsulinism. In this case, Dr. C. C. Evans of the Department of Electrophysiology at Belmont Hospital considered the record indicative of idiopathic epilepsy.

After observing the effects of varied diets on the patient's symptoms, it was decided that exploration of the pancreas was justifiable, and Mr. Andrew Desmond operated on 12.1.54. No tumour was found and subtotal pancreatectomy was performed. Blood-sugar estimations were carried out during the operation (Fig. 3). From the commencement of the operation a 15% glucose drip was given. When the subtotal pancreatectomy was completed this was changed to 5% glucose and later to saline. Comparing Figs. 2 and 3 it appears that removal of part of the pancreas had prevented the fall of blood sugar after the first hour of continuous intravenous infusion. Because it was known that intravenous glucose caused a fall of blood sugar after about an hour, it had been decided not to give glucose until about an hour before the actual removal of the pancreas.

During the weeks after operation the patient was greatly improved. His attacks of *petit mal* recurred and suppressive treatment with phenobarbitone was re-commenced. He was quite confident that the symptoms were different from those he had experienced before operation. After several weeks the oral glucose tolerance curve and the curve during continuous intravenous glucose were repeated: Figs. 1 and 2 show these curves compared with the pre-operative results.

Thirty sections of the part of the pancreas removed were examined without any abnormality being detected.

Some weeks after discharge from hospital the patient had symptoms suggestive of a recurrence and it was feared that after all a small adenoma in the head of the pancreas had been missed, but these symptoms subsided and further blood-sugar studies were satisfactory.

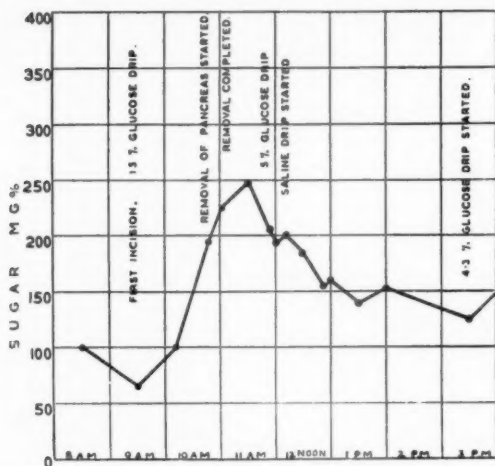


FIG. 3.—Day of operation.

The case lacks some of the classical features of organic hyperinsulinism in that the attacks were not invariably associated with a very low blood sugar and they were not dramatically relieved by giving sugar. Although this last is the third of "Whipple's triad" of diagnostic symptoms for organic hyperinsulinism, as giving sugar results in a fall of the blood-sugar level, it may be wrong to place too much emphasis on this phenomenon.

All who have described these cases have stressed the facts that differential diagnosis from epilepsy and hysteria may be difficult. Sir Henry Cohen in his Moynihan Lecture for 1949 puts "Epileptiform attacks" and "Neuroses and Psychoses" as the first two in his list of differential diagnoses. It is possible that this patient has true epilepsy, combined with hyperinsulinism. If that is so, then it is possible that attacks of hypoglycaemia may have been the precipitating factor leading to epileptic attacks.

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COHEN, H. (1950) *Am. R. Coll. Surg. Engl.*, 6, 3.

**Scleroderma with Pulmonary Involvement and Chronic Bronchitis.**—J. J. Y. DAWSON, M.C., M.D., M.R.C.P. (for H. NICHOLSON, F.R.C.P.).

A. D., male aged 56, employed as a bus driver in London, was admitted to the Brompton Hospital under the care of Dr. H. Nicholson on February 8, 1954. He gave a history of winter cough for ten years which had never been very troublesome. In September 1952 he first noticed numbness and coldness of the fingers, when driving his bus. Raynaud's disease was diagnosed and he gave up driving. In December 1952 he suffered an acute illness with mild fever, increased cough and purulent sputum and right-sided pleuritic pain. Dyspnoea was first noticed at this time. He was given penicillin; the cough and sputum improved but he remained breathless.

In the autumn of 1953 he noticed swelling and stiffness of both forearms. In December his customary bronchitis became worse and in February 1954 he was admitted for investigation and treatment.

*Family and past history.*—Not relevant.

*On examination.*—General appearance normal. Fingers, livid, moist and uniformly swollen, with limited flexion. The skin of the forearms, neck and anterior chest wall was thickened and stiff without atrophy. The skin elsewhere was normal.

*Chest.*—Restricted movement. Signs of chronic bronchitis. Other systems normal.

*Special investigations.*—Sputum 2 oz. daily, purulent. Culture: *H. influenzae*. E.S.R. 12 mm. in the first hour (Westergren).

Chest X-rays (27.1.53) showed heavy "vascular" shadows at both bases, which became heavier during the following year. By February 1954 both lungs showed diffuse reticulation with many small "cysts" up to 5 mm. in diameter, especially at the bases (Figs. 1 and 2).

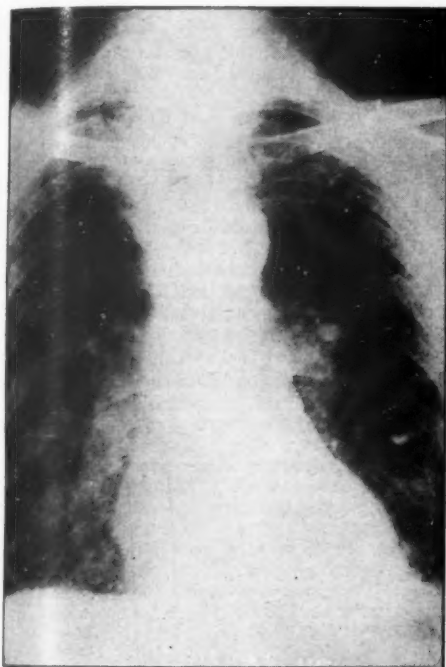


FIG. 1.—Chest X-ray (12.2.54) showing diffuse reticulation with many small "cysts" up to 5 mm. diameter.



FIG. 2.—Enlarged section of right lung to show abnormal shadows.

*Lung function tests* (Dr. Frank Prime) 18.2.54.—The vital and total lung capacities were slightly reduced. The mixing curve was normal. The resting ventilation was raised. There was slight suboxygenation (90% saturation) of the blood at rest and after exercise, with  $\text{CO}_2$  retention and an increase of the alveolar arterial gradient (18.0 mm.Hg).

*Barium meal:* Oesophagus, stomach and duodenum normal on routine examination.

*Liver biopsy* normal.

*Skin biopsy:* Section shows throughout the corium swollen collagen bundles separated by oedema with a scanty inflammatory cellular infiltrate. The appearance is that of the early stage of scleroderma.

*Muscle biopsy* normal.

*Progress.*—26.2.54: Oral cortisone 200 mg. daily was given and after two days the stiffness of his hands improved. Within two weeks he was able to move the fingers normally, especially fine movements which had previously been impossible.

Penicillin 1 mega unit b.d. was tried for one week without effect on the bronchitis. Oxytetracycline 0.5 gram six-hourly was then given from 4.3.54. After two weeks he developed diarrhoea and the drug was stopped. The sputum which had become mucoid again contained pus. Penicillin, 4 mega units daily, was given for a further twenty-one days without effect. Tetracycline 1 gram eight-hourly was substituted. The sputum volume decreased to  $1\frac{1}{2}$  oz. and became mucoid. At the end of April the dose of cortisone was reduced by 25 mg. every two days to 75 mg. daily. The dose of tetracycline was lowered to 0.5 gram b.d.

The patient left hospital on May 12 and continued with the drugs through the summer, attending the out-patient clinic every two weeks. He returned to his job as a lift man. His sputum, less than 1 oz. daily, remained mucoid throughout the summer. The skin of the hands became thicker again and he found difficulty in undressing; the vasospastic symptoms which had subsided in hospital also returned. The skin over the mandibles previously unaffected became thickened.

The appearances of the chest radiograph were unaffected by cortisone and no significant change was seen in a second skin biopsy taken two months after the start of cortisone treatment.

*Comment.*—27 examples of scleroderma affecting the lungs were collected from the literature by Hayman and Hunt in 1952. Usually the lungs are involved after the disease has become obvious elsewhere, and there is then no difficulty in making the diagnosis. This case is unusual in that the lung changes were present only a few months after the onset of vasospastic symptoms and before permanent skin changes were apparent. Only 7 such cases have been described. The development of many small cysts in the lungs is uncommon; Church and Ellis (1950) have described two examples. The pathological changes in the lungs have been described by Getzowa (1945). They consist at first of patchy thickening of the alveolar walls by collagen bundles. Later, clumps of hyalinized alveoli are formed with intervening emphysema and the blood vessels become narrowed and hyalinized. The connective tissue of the bronchi is sometimes involved.

This patient's chronic bronchitis, which preceded the onset of scleroderma and is apparently not connected with it, was due in part to infection with *H. influenzae*. It responded well to tetracycline but not to large doses of penicillin. The transient improvement of the scleroderma affecting the hands when cortisone was given was presumably due to the control which this drug exerted on the oedema and inflammatory reaction in the skin. The thickening and stiffness of the skin returned after a few months and the chest radiograph was not improved; it seems unlikely that cortisone has had any but the most fleeting effect on the course of the disease.

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HAYMAN, L. D., and HUNT, R. E. (1952) *Dis. Chest*, 21, 691.

## Section of Medicine

President—Professor Sir HENRY COHEN, M.D., D.Sc., LL.D., F.R.C.P.

[October 26, 1953]

### The Evolution of the Concept of Disease

#### PRESIDENT'S ADDRESS

By Professor Sir HENRY COHEN, M.D., D.Sc., LL.D., F.R.C.P.

"THE very purpose of philosophy", wrote Whitehead in his "Adventures of Ideas", "is to delve below the apparent clarity of human speech". The dominant trends in contemporary philosophy have been fashioned and profoundly influenced by semantic studies; they reject the Baconian precept that the study of words is "the first distemper of learning".

In medicine there are innumerable examples of words whose meaning has altered with the passage of time and increasing knowledge. For example, "artery" persists from the pre-Galenic days when that vessel was thought to contain air ( $\alpha\acute{\iota}\rho$  = air;  $\tau\eta\rho\epsilon\acute{\iota}\nu$  = to keep); the "phrenic" nerve supplied the diaphragm which was then regarded as the seat of the mind (Gk.  $\phi\rho\acute{\eta}\nu$  = mind); the "pituitary" gland owes its name to the mistaken notion that it secretes the nasal mucus (L. *pituita* = phlegm); the very different pathological states of osteomyelitis and myelitis share their common etymology from the days when the spinal cord was thought to be the bone-marrow (Gk.  $\mu\epsilon\lambda\acute{\lambda}\acute{o}\varsigma$ ) of the vertebral column. These words, and an infinity of others, have varied in meaning with changes in contemporary knowledge and theory; their colour and content reflect the knowledge of the times in which they were introduced.

The word "disease" is no exception to this general rule. The notion or concept which it conveyed has varied with the ideas held about the nature of disease through the ages. The differentiation of disease as *dis-ease*, with its pain and suffering contrasted with health (O.E. *hal* = whole) has been recognized from the earliest times, though its existence has been denied by the Stoics in ancient times and, more recently, by quasi-religious cults. Primitive man was not deeply concerned with the nature or cause of disease. He sought its cure. And his purpose was not wholly selfish; sympathy for his fellows is revealed in his writings as one of the dominant human instincts.

The cures which he elaborated were based on crude supernatural magical doctrines, all of which, however, profoundly influenced later thought. Of these principles, those most widely known were the doctrines of *similars*, of *signatures*, of *analogy*, and of *contagion*.

The doctrine of *similars* was based on the principle that objects or circumstances similar in shape, colour, or sequence of events to those preceding or resulting from disease were effective in its treatment. For example, the appropriate remedy for greying hair was stewed raven because of its deep black features, whilst yellow birds were useful for jaundice.<sup>1</sup>

Those who based their practice on the doctrine of *signatures*, and it had a long sway, claimed that plants and animals have distinctive marks which indicate their medicinal properties. Thus trefoil was used in heart disease; the yellow celandine in jaundice; cyclamen for ear disease; flowers of the lily for gout; the roots of bryony (which resembled a swollen foot) for dropsy; thistle for a stitch in the side; walnut shells for head injuries; the spotted skin of the lizard for tumours. This doctrine was later to be the main basis of the therapeutic systems of Paracelsus and Culpeper.

The doctrine of the *analogy* had a more modern ring. The behaviour of ailing animals was observed, the food they took, whether, where and when they rested. Similar measures were then adopted in cases of human illness. Later, analogy was extended to ill people. Special attention was paid to what happened to those who recovered. From analogy there came many useful contributions to knowledge; but it saw the birth in medicine of the *post hoc ergo propter hoc* fallacy whose baneful effects still influence treatment.

The doctrine of *contagion* was more recondite and took account of the alleged cause of disease. The object used in treatment was one which had been associated with this cause, for example, moonstone in mental disorders.

Except for the doctrine of contagion none of these principles of treatment was based on theories concerning the nature of disease. From the earliest times to the present day two main concepts have dominated all writings on the nature of disease. These are (i) disease as a distinct entity; when a healthy man A falls ill he becomes A plus B, where B is "a disease". This view maintained that there are innumerable Bs, each with its individual and recog-

nized character. This doctrine differs from that of Hahnemann's *similars*—*similia similibus curantur*—in that here a drug is advocated because it gives symptoms and signs similar and peculiar to those which the patient manifests. Hippocrates reveals his acceptance of this doctrine in the use of veratrum, but his writings show him as an eclectic who did not confine his therapy to one system.

nizable characters. And (ii) disease as a deviation from the normal; a healthy man  $A$ , through the influence of any number of factors ( $x_1, x_2, x_3 \dots x_n$ )—physical or mental—is changed and suffers; he is dis-eased ( $A$ ). The appropriate formula is  $A^{x_1, x_2, x_3 \dots x_n} \rightarrow A$  when ill.

Many terms are used to cover these two concepts, e.g. *ontological*—indicating the independent self-sufficiency of diseases running a regular course and with a natural history of their own, as opposed to the *biographical* or *historical* which records the history of the patient. Other names arise from the founders of the schools of thought which appear to have given these concepts birth, e.g. *Platonic* and *Hippocratic*; from the site of their main temples, *Cnidian* and *Coan*; from the philosophies from which they are primarily derived—the contrasting *realist* and *nominalist*, *rationalist* and *empirical*, *conventional* and *naturalistic* schools. The names are of little importance. The two notions varying a little in content and occasionally overlapping have persisted, the dominance of the one or the other at different epochs reflecting either the philosophy of the time or the influence and teaching of outstanding personalities.

The earliest views on the nature of disease, its cause and its cure by eradicating the cause, stem from the fact that in the early history of mankind religion, philosophy, and medicine were a single discipline. Religion recognized the multiplicity of gods, both good and evil; and philosophy accepted the influence of inanimate bodies, especially the sun, moon, and stars, on living things. Thus arose the most primitive concept of the nature and cause of disease, namely that it is due to the influence of evil spirits, a concept appropriately labelled *demoniacal*. But this idea had at least five variants. The simplest was that of an evil spirit entering the body directly and therein pursuing its nefarious purpose. For this, the appropriate prophylactic was the amulet, which took various forms, especially bracelets. Modern counterparts are by no means rare; witness the carrying of a new potato in the pocket or wearing a ring to ward off rheumatism. Once the spirit had entered the body, treatment consisted of exorcism by appropriate incantations, such as that of Marcellus in the fourth century who is recorded as treating an ulcer of the eye by reiterating, "Fly, fly, a barley corn is pursuing you". One of the earliest known surgical operations—trephining of the skull—owed its rationale to this concept. Its intent was to facilitate the expulsion of the evil spirits from the diseased body.

But the evil spirit might indeed be a messenger of the gods and it then had to be placated or cajoled by burnt offerings or sacrifices. Or a human enemy might possess supernatural power influencing the diseased person; his machinations were to be warded off by sorcery and spells. The idea of the "soul"—an *alter ego*—which arose from the attempt to interpret such phenomena as dreams, the shadows of objects and their reflections in water—gave rise to the idea that disease might be associated with offending spirits of the dead. It was from this that stemmed the family loyalties and ancestor worship of primitive peoples. The idea of the transmigration of "souls" was used not only in interpreting disease, but also for therapeutic purposes. The young lay with the old so that the more vital spirit of the young might pass over to the old. I well recall seeing, some twenty years ago, an Armenian patient with grave jaundice, and on entering the room, there was a repellent odour which I discovered to be due to a pigeon which had been slit open whilst alive and applied directly to the chest of the patient so that its "living principle" might enter the patient and sustain her.

The idea of diseases as separate entities springs in part from this demoniacal concept and was fostered by the description of "diseases" by the ancient writers. Hippocrates wrote essentially of disease in individuals—a biographical approach, and Aretaeus, the Cappadocian, in the second and third centuries A.D., gave careful pictures of patients with pneumonia, pleurisy with effusion (*empyema*), diabetes, tetanus, elephantiasis, the aura of epilepsy, cross paralysis from brain injury, &c. But these were records of individual cases. It is not until the ninth century that we detect the early glimmerings of generalization. It was then that Rhazes of Persia differentiated smallpox and measles.

After this many separate "diseases" began to be described. Glisson's description of rickets in 1650 is among the classical examples, and shortly after Glisson came the greatest of ontologists, Thomas Sydenham (1624–89), the "English Hippocrates", for whom diseases were "to be reduced to certain and determinate kinds with the same exactness as we see it done by botanic writers in their treatises of plants", and possessing "certain distinguishing signs which Nature has particularly affixed to every species". Illustrative of Sydenham's outlook is the following quotation:

"Nature, in the production of disease, is uniform and consistent; so much so, that for the same disease in different persons the symptoms are for the most part the same; and the selfsame phenomenon that you would observe in the sickness of a Socrates you would observe in the sickness of a simpleton. Just so the universal characters of a plant are extended to every individual of the species; and whoever (I speak in the way of illustration) should accurately describe the colour, the taste, the smell, the

figure, etc., of one single violet, would find that his description held good, there or thereabouts, for all the violets of that particular species upon the face of the earth."

In the second half of the eighteenth century, classification of "diseases" became an obsession of medical writers largely due to the impetus given to taxonomy by Linnæus' "Systema Naturæ (1735)". This included the critical sentence—"Species tot sunt diversae quot diversae formae ab initio sunt creatae". In 1768 Francois Boissier de Sauvages, botanist and physician, published a detailed "Nosologia methodica sistens morborum classes, genera, et species" based on Linnæus. He divided "diseases" into ten classes, subdivided these into forty orders, the orders into genera, and the genera into species—in all 2,400. Cullen and others were later to embellish this with even greater detail.

The concept of disease as a "clinical entity" still dominates much of our textbook descriptions, as illustrated by the so-called classical pictures of typhoid fever, influenza, disseminated sclerosis, and the rest. Many of these are little more helpful in diagnosis than would be a composite portrait of a Cabinet or a Test Team in revealing whether a given individual is a member of either. And we still seek for pathognomonic signs as short cuts to diagnosis, e.g. the staccato speech, intention tremor, and nystagmus of disseminated sclerosis; the thirst, polyuria, wasting, and glycosuria of diabetes mellitus; the goitre, proptosis, tremor, and tachycardia of Graves' disease. And we are even happier when these pathognomonic signs or specific tests are revealed by the exact instruments of a clinical laboratory, by X-rays or by a whole gamut of electrical recording machines. This way lies simplicity and directness; this way labour, time, and thought can be conserved. But this way lies also error and unreason.

The concept of disease as a deviation from the normal owes its birth to the abstract nature of Greek thought. For the Greeks, reason was the master. Observation of Nature was a low menial who could be disregarded if she contradicted the master. Indeed, pervading the whole of Greek thought is the attempt to conceive Nature without an adequate knowledge of its parts; to generalize from inadequate particulars. In the abstract realms of mathematics the results were profound and indeed astounding when contrasted with the scientific knowledge of the age. There was, indeed, a perverse trend on the part of Greek philosophers to transcend experience by dialectics. But this was not confined to the Greeks. Indeed, as Sarton has written, history suggests that this is an intrinsic defect of the human mind. We have seen it in our own times in the works of such physicists as Eddington who have held that "the structure of the universe can be established on an *a priori* basis because of the structure of our mind".

In the fifth century B.C. Empedocles conceived the whole of Nature as derived from the four elements—fire, earth, air, and water. In the later works of Hippocrates and Aristotle, we observe the development of the idea of four associated qualities—heat and cold, dryness and moisture, and of the four humours of the body—blood, phlegm, yellow bile and black bile.

It was Plato in "Timæus" who first asserted that health was harmony, and disease discord of these four humours. He postulated that discord might arise from (i) an unnatural excess or defect of the four humours (a quantitative change); (ii) a change in their natural place (site); and (iii) the humours being of the wrong kind (a change in quality). But Plato argued also that disease might arise from a disturbance of the normal proportions of body and soul; when the soul is dominant, it leads to convulsions and "fills with disorders the whole inner nature of man"; but if the body is dominant, then the soul becomes dull, stupid, and forgetful—ignorance and apathy result. It is in "Timæus" that Plato's classification of disease based on these general principles is given.

Plato's theories led to the school of doctors which Galen labelled *Dogmatists*, which existed for at least a century after the death of Hippocrates. Its system had a twofold basis. Firstly, the *humoral* theory of disease which was to dominate medicine for 2,000 years was expanded, and provided the explanation for such later "diseases" as rheumatism (a flow of abnormal humours), gout (drops of humour appearing in abnormal situations), melancholia (the depression caused by an excess of black bile); and the splenic and choleric disposition. Secondly, it relied on the magic of Pythagorean numbers, especially 7, e.g. the Dogmatists stressed the significance of multiples of 7 in the appearance of the second teeth at 7 years, puberty at 14 years, and hair on the beard area at 21 years.

During the second and third centuries B.C., the teachings of Aristotle, and their emphasis on observing nature, were exerting greater influence, and with this arose the school of *Empiricists*. Their rise was not simply a reaction to the rationalism of the Dogmatists. Two other happenings played a prominent role. Firstly, at that time Greece was extending her commerce to other Mediterranean countries, where were heard tales of wonder about the efficacy of drugs and the effects of poisons. And secondly, Pyrrho and the Sceptics were wielding greater influence. They taught that it was impossible to know the true nature of things for perception shows us objects not as they are, but as they appear; so we must

suspend judgment, since reason itself is futile (except apparently when reason seeks to demonstrate its own futility!). Hence the Empiricists observed the workings of Nature; unlike the Dogmatists, they did not aspire to unmask by reason the final causes of the things observed. Their observations were concerned essentially with treatment and it was here that their journeys abroad enriched their therapeutic resources. Their knowledge of the nature and cure of disease was based on the tripod of *autopsy*, *history*, and *analogy*. For them, *autopsy* covered the patient's observations on himself; *history* meant learning from others—from teachers and from books; *analogy* implied observing similar events in others. Later, the Empiricists added a fourth method of attaining knowledge—*epilogism*—by which they meant inferring preceding events from present symptoms. But to their credit it must be conceded that in their teaching is to be found the germ of the idea of a "syndrome", and indeed it was on this that their analogies were based, and they defined disease as "a union of symptoms which are observed always in the same way in the human body", without, however, giving "disease" a strictly ontological interpretation. For the Empiricists, anatomy appeared quite unnecessary and since they had no means of distinguishing *propter* from *post*, charlatanism was rife in their search for specifics, and the doctrine of signatures held unimpaired sway.

Rational Greek medicine reached its purest exposition in the school of the Methodists who applied the principles of Epicureanism to medicine. This school originated with Asclepiades of Bithynia (born in 124 B.C.), but it was more fully developed by his pupil, Themison of Laodicea (123–43 B.C.). The Methodists believed that the body of man was an infinity of atoms (small particles) and pores (the spaces between the particles). If the size, weight, shape, position and movement of the particles were normal, then health (symmetry) resulted. Themison held that disease resulted from disturbance of the pores. He recognized three communities of disease, (i) excessive relaxation or enlargement of the pores, (ii) contraction of the pores, and (iii) a mixed group. Both diagnosis and treatment were simple. If the disease resulted from relaxation of the pores, astringents such as cold baths, vinegar, alum, lead, and chalk were indicated; whilst if contraction of the pores caused disease, then laxatives such as venesection, cupping, leeches, poultices, fomentations, and warmth were called for. They did not accept the doctrine of signatures; their therapeutic maxim was *contraria contrariis curantur*. The Methodists claimed to be the only begetters of the true faith. Like many who have devised systems since, they despised earlier knowledge and held that there was no medicine of any importance known before them. What had been taught by earlier schools had been they held inaccurate, and consequently unduly complicated and prolix. Indeed, one of the protagonists of Methodism, Thessalus of Lydia, reversed the Hippocratic aphorism, holding rather that "art is short and life is long", and maintained that all medicine could be taught in six months. On a monument in the Appian Way he styles himself, "Conqueror of Physicians".

Anatomy and physiology in any modern sense had no place in the practice of the Dogmatists or the Methodists. But this practice was systematized and had a strong attraction for the rational mind.

Since their time, innumerable systems have had their day and then ceased to be. Even after Sydenham's appeal in the seventeenth century for a return to the study of the natural history of disease, many systems were evolved during the eighteenth century which reflected the ideas of the Methodists. In each of these the central idea was that of health being due to the just balance of two opposing tendencies; disease resulted from their imbalance. Two systems which exerted considerable influence were those of John Brown (1735–88) and of Broussais (1772–1838). The Brunonians regarded tone as the dominant characteristic of the body. Disease was *sthenic* (due to excessive tone) or *asthenic* (due to lack of tone). For the former, opium and for the latter, alcohol were the appropriate, and to the patient most acceptable, remedies. For Broussais the "irritability" of tissues was what determined health or disease. He was strongly opposed to delineating clinical pictures of disease and describing their "typical" course. "Those groups of symptoms", he wrote, "which are given out as diseases are metaphysical abstractions which by no means represent a constant unchangeable morbid condition. . . . They are factitious entities (*entités factices*)."

Typical of the kind of system developed during the eighteenth century was that of Theophilus Lobb ("Medical Principles and Cautions", 1751) who wrote as follows:

"The Causes of Diseases in general are the following, viz.

- i. Some Excess in the Quantity of one or other of the Animal Fluids; that is, an Excess either in the Quantity of the Blood, or of the Lymph, or of the nervous Liquid; which three general Fluids are always moving in all Parts of the Body.
- ii. Some *wrong Quality* of them.
- iii. Some *deficiency* in the Quantity of one or other of them; Or,
- iv. Some *Combination* of these causes.

The Cause of every Disease that can happen to the human Body (how manifold soever they may be) is comprehended in one, or other of the Heads mentioned."

Those familiar with the history of endocrinology and of the "stress" syndrome will recognize from these examples the forerunners of the general theory pervading more modern concepts.

The significance of anatomy and physiology in medicine and in the interpretation of disease was but little appreciated before the nineteenth century. Surgery, it is true, had benefited from the studies of the early anatomists and such operations as amputation, lithotomy, and the excision of tumours were designed on the basis of the anatomical knowledge then available. But even Vesalius' monumental work ("*De Humani Corporis Fabrica*", 1543) and Harvey's classical demonstration of the circulation of the blood ("*Exercitatio De Motu Cordis*", 1628) had but little direct influence on the rational practice of medicine. The emphasis, however, which these works placed on the lever-like action of muscles and joints, and the analogy of the circulation with pumps, valves, and conduits led to the concept of medicine which treated the body as a machine. The influence of Newton's "*Principia*" (1687), embodying the simple mechanical laws governing the universe, lent weight to this view. Indeed, Newton's work forms the basis of an interesting but neglected book by Thomas Morgan on "*Philosophical Principles of Medicine*" (1725). This book is divided into three parts. The first is "a Demonstration of the general Laws of Gravity with their Effects upon Animal Bodys". The second deals with "the more particular Laws which obtain in the Motion and Secretion of the vital Fluids, applied to the principal Diseases and Irregularitys of the Animal Machine." And the third describes "the primary and chief Intentions of Medicine in the Cure of Diseases, problematically propos'd and mechanically resolv'd". In this preface, Dr. Morgan stresses

"That the animal Body is a pure Machine and that all its Operations and Phaenomena with the several changes which happen to it are the necessary result of its Organisation and Structure". This, he says, "is now generally known and confirmed beyond all contradiction by the modern Observations and Improvements in Anatomy". He explains "how necessary it is for a Physician to be well acquainted with the Principles and Laws of Motion together with the Constitution and Structure of animal Bodys and the application of one to the other. For since the animal Body is a Machine and Diseases are nothing else but its particular irregularitys, Defects and Disorders, a blind Man might as well pretend to regulate a piece of Clockwork, or a deaf Man to tune an Organ, as a Person ignorant of Mathematics and Mechanism to cure Diseases without understanding the natural Organisation, Structure and Operations of the Machine which he undertakes to regulate".

Pitcairn and Mead were later among the staunch adherents and exponents of these iatromechanical doctrines.

The role of chemistry in medicine was first emphasized by van Helmont (1577-1644). He and his successors investigated the chemistry of the secretions and ferments of the body, whilst Boyle and Hooke were contributing to the knowledge of respiration by their researches on air. On the work of these chemical pioneers developed the iatrochemical school which was firmly established by the beginning of the eighteenth century.

Before long, however, a reaction to the iatromechanical and iatrochemical schools appeared. It stressed that mechanism and chemistry were not enough. Regard had to be paid to the "soul" in medicine. This movement found its early exposition in the works of Georg Ernst Stahl (1660-1734), who revived a Cartesianism which taught that all vital movement is derived from the soul, and that the body is simply a passive agent guided by this immortal soul. Friedrich Hoffman (1660-1742), a strong advocate of similar views, emphasized that the universe is pervaded by a vital substance "finer than all other matter, but not exactly spirit, soul or mind"; this subtle substance he thought maintained the body in a state of tonic equilibrium and he then emphasized, as did the Methodists, that disease resulted from an excess of this tone (when sedatives were indicated) or a deficiency (when tonics were indicated). Excess of tone, he held, was usually an acute process, whereas deficiency was chronic. But Hoffman was not prepared to abandon wholly the humoral theory and he taught that there were changes in humoral balance which required alternatives for their correction and that there might also be faulty excretion of the humours which demanded evacuations.

During the eighteenth century not only normal anatomy but also the anatomy of disease rapidly advanced. For the first time with Morgagni (1682-1771) in his "*De Sedibus et Causis Morborum*" (1761) came a clear attempt at correlating clinical observation with post-mortem findings, thus laying the foundations of pathology as a fundamental medical science. The clinicopathological correlations then established acquired an added importance when, in the nineteenth century, Virchow related clinical syndromes not simply to organs but to cellular systems, such as the blood and haemopoietic tissues, which might be distributed through many organs. They continue to play an important part in more recent work, for example, in that of Klinge on rheumatism as a manifestation of connective tissue disturbance, and of Klemperer's correlation of the collagen diseases.

In 1828 with Wöhler's synthesis of urea occurred a revolution in the approach to vitalism. Then for the first time a product of living matter was synthesized in the laboratory. The

instruments of physics and chemistry, rapidly increasing in sensitivity and complexity, were during the ensuing decades turned to the study of disease. Normal values were determined and deviations from the normal recognized. Hyperchlorhydria and hypochlorhydria, hypertension and hypotension, polycythemia and anaemia, were now capable of recognition and quantitative assessment. But minds still shackled with the concept of diseases as "entities" interpreted even these changes in terms of "diseases".

The distinctive contribution of the nineteenth century, however, to the concept of disease was the recognition of its causes. Bacteria as the necessary and specific causes of such diseases as typhoid, tuberculosis, cholera, were unmasked; the significance of endocrine imbalance, of nutritional deficiencies, of genetic influences was soon recognized; the part played by social, occupational, and economic factors, and the psychological contribution to the aetiology of disease were all made clearer.

With this background we are in a position to appraise the present status of the two concepts of disease which we earlier recognized as pervading the history of medicine in the past 3,000 years.

We no longer regard diseases as being capable of reduction "to certain and determinate kinds with the same exactness as we see it done by botanic writers in their treatises on plants" and possessing "certain distinguishing signs which Nature has particularly affixed to each species" (Sydenham). But "disease" labels remain convenient symbols in those recurrent clinical patterns which are frequently isomorphic, as for example, in acromegaly, though they are less satisfactory where the variability of the clinical picture is much more marked, as, for example, in rheumatoid arthritis. The dangers which the "entity" concept carries are (i) that it promotes a "penny-in-the-slot machine" approach to diagnosis by seeking for pathognomonic signs especially the short cuts of the laboratory or instrument; (ii) that it suggests that diagnosis is arrived at by comparing an unknown with a catalogue of knowns: the method of recognizing an elephant by having seen one before; (iii) that it reduces thought to a minimum; (iv) that it is of little help and may be positively misleading where the disease process varies significantly from the usual, and, (v) that it leads to all those dangers associated with a label which Cowper implied when he wrote of those—"who to the fascination of a name, Surrender judgment, hoodwinked".

The second concept—deviation from the normal—interprets disease rationally in terms of anatomy and physiology. The simplest changes are *quantitative deviations from the normal* such as hypertension, menorrhagia, hypoglycaemia, macroglossia, anencephaly. It is, of course, important to recognize that the normal is a range and not a rigid figure (we recognize this in regard to the length of the nose but less frequently with regard to the blood pressure!); and that the range varies with age, sex, number, site. These simple quantitative deviations from the normal are, however, commonly combined in constantly recurring patterns (isomorphism); these we label "syndromes". Of these, three groups are clearly recognizable. The first is *anatomical*; e.g. staccato speech, intention tremor and nystagmus are manifestations not of disseminated sclerosis but of a disorder of the cerebellar mechanism; the vomiting of huge quantities of fluid free from bile and containing food taken twenty-four hours earlier is evidence of pyloric obstruction. The second group of syndromes are *physiological* (and here we include also *psychological*); thirst, wasting, polyuria, glycosuria are the signs not of a disease, diabetes mellitus, but of impaired carbohydrate tolerance. The division into anatomical and physiological is somewhat artificial; physiological disturbances may well reveal an anatomical site of disease; for example, the disturbances of sensation which localize disease in the parietal lobe. Thirdly, the syndrome might indicate *pathological* changes, e.g. redness, swelling, heat and pain as evidence of inflammation; or *aetiology*, e.g. the Hutchinsonian triad as evidence of congenital syphilis.

It is this concept which should dominate our teaching and our approach to medicine. In brief it may be stated thus: (a) disease indicates deviations from the normal—these are its symptoms and signs; (b) symptoms and signs are commonly found to recur in constant patterns; these are the "syndromes" or "symptom-complexes"; (c) these syndromes always indicate one or more of three aspects of disease (1) its site, (2) associated functional disturbances, (3) causative factors in terms of (i) morbid anatomy, physiology and psychology, and (ii) aetiology.

Galen desired that every true physician should be also a philosopher. Philosophical enquiry in medicine is apt to be regarded as an arduous eccentricity for which few physicians in our time have had either the opportunity or the inclination. Yet it is a worth-while pursuit, for a knowledge of the history of ideas has a moderating influence. It helps to keep a balance between undue dogmatism on the one hand and undue scepticism on the other; and above all in revealing the thoughts and expounding the works of some of the greatest minds in human history, it inculcates a humility which is the surest shield against intellectual arrogance.

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## Section of Orthopædics

President—R. W. BUTLER, M.D., M.Chir., F.R.C.S.

[October 5, 1954]

### Acute Osteomyelitis of the Right Femur.—G. N. GOLDEN, F.R.C.S.

Baby G. A. First seen on July 14, 1954, then aged 5 weeks. The mother said that the child had been quite well until the morning of July 14, when she had noticed a swelling in the region of the right hip. The child had cried the previous night a great deal. The obstetrical history was normal; she was the first child and breast fed; progress and weight were satisfactory.

The child seemed in good general condition; temperature 99.2°. A very large, tender swelling involved the right hip region and most of the right thigh with a large fluctuant abscess in the upper part of the thigh. There was no evidence of umbilical sepsis.

The child was admitted to hospital and a large amount of thick pus was evacuated from subcutaneous and subperiosteal abscesses, which spread down as far as the lower third of the shaft. The cortical bone exposed was found to be much softened in the upper third. Several drill holes were made but no pus under tension was found. No attempt was made to aspirate the hip-joint. The wound was lightly packed with vaseline gauze for a few days.

Cultures of the pus on opening the abscess showed a heavy growth of coagulase-positive *Staph. aureus*. W.R. and Kahn negative.

The child had fifteen days in hospital on penicillin. She was breast fed throughout. Her weight remained level for the first six days and then steadily rose. Her condition remained excellent. The swelling and tenderness of the thigh rapidly decreased and healing was almost complete on discharge from hospital. Since then the child has regained vigorous health and movements of the hip-joint are free and painless.

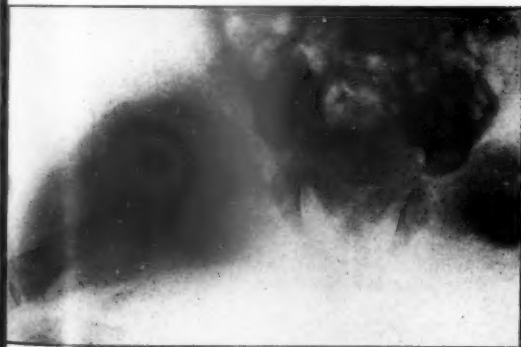


FIG. 1.—Acute osteomyelitis of right femur in child aged five weeks, on admission.



FIG. 2 (right).—The same case two weeks later.

Fig. 1 is the X-ray taken on admission. Fig. 2 is that of an X-ray taken fourteen days after the child's admission, showing the very severe destructive process involving almost the whole femoral shaft but surrounded by a strong and rapidly growing involucrum. It appears to stop sharply a few millimetres from the epiphyseal line and the ossific nucleus of the developing capital epiphysis on this side appeared a little earlier than the one on the left.

The chief interest of this case is the very severe and extensive osteomyelitis as shown in the X-ray film (Fig. 1), in contrast to the relatively benign clinical course and rapid recovery. In view of the frequency with which osteomyelitis affecting the upper end of the femoral shaft in infants involves the hip-joint it is remarkable that such a severe case should have left the joint and the capital epiphysis entirely unaffected.

M.R.

**Infantile Cortical Hyperostosis.**—G. N. GOLDEN, F.R.C.S.

Baby C. A. S. First seen on March 18, 1954, then aged 5 months, with a history that for three days she would not move the right leg. There was no history of injury and the child had apparently been quite well, apart from a cold which had developed a day or so before examination. The mother had noticed swelling of the right thigh and that the child cried when it was moved or touched. There was no temperature and at the first examination nothing abnormal was found anywhere except the tender swelling of the right thigh.

Fig. 1 shows a thin line of periosteal bone formation along the greater part of the shaft of the right femur, stopping short of the metaphysis at each end. No other abnormality was detected in the femur itself or of the pelvis or the other bones of the lower limbs.



FIG. 1.—Infantile cortical hyperostosis of right femur: appearance at early stage.



FIG. 2.—The same case four weeks later.

The possibility of scurvy was considered, although the child was breast fed and there were no other clinical signs, the gums being quite normal. Ascorbic acid was given, 25 mg. five times a day.

The child was seen again on April 8, when the periosteal shadow had increased markedly but it was still limited to the same area.

She was admitted to hospital and was found to have a very slight pyrexia which remained between 99 degrees and 100 degrees rectally for eight days. There was a tense swelling of the right thigh throughout its whole length, which was very tender. Apart from the fact that she did not like any examination of the thigh she seemed in very good spirits and health.

Fig. 2 shows the maximum development of new subperiosteal bone around the right femur. No other bones were affected.

The Wassermann reaction was negative. Hb was not estimated. W.B.C. 19,300—39% polymorphs, 52% lymphocytes, 6% monocytes. Urine was normal.

The tenderness and swelling of the right thigh gradually decreased and on May 13 no tenderness was noticeable and there was no appearance of swelling. At no time was there any redness or feeling of heat over the right thigh and movements of the joints above and below were easy, although palpation of the thigh caused the child to cry.

On August 26 the child was crawling actively, and appeared to have no pain or tenderness of any kind. X-rays then showed considerable absorption of the extra bone and gradual thinning and absorption of the original cortical bone. She has remained in excellent health.

This condition of cortical hyperostosis in infants has been reported frequently during the past few years since it was originally described (Caffey, J., and Silverman, W. A., 1945,

*Amer. J. Roentgenol.*, 54, 1). The 4 cases they described differed from my case in that they all showed extensive affection of the skeleton and a more severe clinical disturbance. Otherwise the X-ray findings of my case coincide closely with their description. The cause of this condition remains obscure and several writers have suggested a virus infection.

The differential diagnosis from subacute osteomyelitis sometimes presents difficulty. The comparison of the clinical and X-ray appearances of these two cases shows clearly the distinctive features of the two conditions.

Mr. Philip Wiles, referring to the case of osteomyelitis of the femur, said that he thought Mr. Golden had got the case rather late, and not early as had been suggested. He himself had had a case of severe osteomyelitis of the femur in a child born a month prematurely; the complaint developed two weeks after birth. Several ounces of pus were aspirated, and the bone was normal again in a few months.

It could not be said that osteomyelitis was now pursuing a more benign course than formerly. The resistance of the patient was probably greater. It used to be a disease associated with poverty and dirt, with the result that in the old days osteomyelitis was very much worse than now.

Referring to the case of cortical hyperostosis he thought that one should hesitate before accepting the statements that this condition had been helped by penicillin; he supposed everyone could furnish an example in point. All the evidence now was in favour of the condition running a non-inflammatory rather than an inflammatory course.

Mr. H. A. Kidd recalled a case of infantile cortical hyperostosis which he saw in 1947, in which penicillin and sulphonamide were quite without effect. Spontaneous recovery occurred after four months in hospital and when last seen in 1951 X-ray showed all the bones had returned to normal.

#### **Sacro-coccygeal Agenesis.**—JOHN ADDISON, F.R.C.S.

T.P., male, aged 18 months.

First seen 21.5.54, referred for opinion on feet. Normal birth. No relevant family history. Brother normal, aged 6.

*On examination.*—He was a well-nourished child of normal intelligence. The spine showed a prominence in the lumbar region. The buttocks were flattened, and there was a depression in the lower sacral area. The lower limbs showed tapering with some valgus collapse of both feet. The innominate bones could not be moved separately. On rectal examination, the lower part of the sacrum was found to be absent, but there appeared to be a firm block of tissue between the posterior parts of the iliac bone. Sensation in the lower limbs was present, and power appeared good.

The child was incontinent of both urine and faeces, and the bowels had to be kept fairly constipated.

He has started to walk and progresses reasonably for his age. X-rays show the sacrum is absent. There is one partially developed vertebral segment, which is probably the 1st sacral element. The hips are in position. The head of the left hip has not yet appeared (Figs. 1 and 2).

Soothill (1954) has reported this case fully.



FIG. 1.



FIG. 2

FIGS. 1 and 2.—A.P. and lateral views show absence of sacrum.

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Mr. F. G. Ward stated that he was acquainted with a similar case requiring operation on the feet. It was that of a boy of 12 who, previously incontinent, was gaining control of micturition.

**Dupuytren's Contracture of Hands and Feet.**—M. H. M. HARRISON, Ch.M., F.R.C.S. (for H. E. HARDING, F.R.C.S.).

A. C., male, aged 46. Carpenter.

The onset of a progressive contracture of the fingers of both hands was noticed three years ago; for the last eighteen months tender lumps have been noted in the soles of both feet. The patient made considerable complaint of discomfort in his feet experienced when walking. There is no family history of a similar condition either of the hands or feet. For the last twelve years the patient has suffered from epilepsy.

On examination, typical Dupuytren's contractures of a moderate degree were found in both hands (Fig. 1). There was a well-defined tender nodular thickening in the medial parts of the soles of both feet underlying the medial longitudinal arches (Fig. 2). The nodules were of various sizes, the largest was approximately 1 in. by 1½ in.; they were not attached to the skin but were fixed deeply and could be moved only across the sole and not in its length. There was no deformity of the toes. The Wasserman and Kahn reactions were negative.

The right foot was operated upon under general anaesthesia and a tourniquet on 19.8.54. The nodules were found to lie in the plantar aponeurosis (Fig. 3) and to have no firm attachment to skin or deeper structures, nor to extend into the toes. The affected part of the central portion of the plantar aponeurosis was excised *en bloc*, without any of the difficulty comparable to palmar aponeurosectomy for Dupuytren's contracture. The wound healed by first intention, and six weeks later the patient was walking well, completely free of pain and tenderness in the right foot; he was anxious to have the same operation performed on the left foot.

On histological examination (Fig. 4) the nodules were found to be composed of a cellular connective tissue with relatively little intercellular collagen; numerous clefts were present throughout this stroma. Preparations stained by the Prussian blue reaction revealed small quantities of free iron adjacent to the clefts.

**Comment.**—Dupuytren's changes affecting the plantar aponeurosis is uncommon; Skoog in his monograph (1948) on the condition refers to about 60 examples that have been described in the literature, and adds another 8 cases of his own. The findings in this patient's feet



FIG. 1.



FIG. 2.

FIG. 1.—Left and right hands showing Dupuytren's contracture. FIG. 2.—The sole of the left foot: there is a circular lump in the subcutaneous tissues underneath the medial longitudinal arch.

appear to be quite typical. It is interesting to note that he is an epileptic; Lund (1941) and Skoog (1948) have drawn attention to the abnormally high incidence of Dupuytren's contracture of the hands and feet in epileptics.

Skoog has elaborated a theory of pathogenesis which indicts trauma as an aetiological factor acting in conjunction with an underlying predisposition to the disease. One of the



FIG. 3.—The sole of the right foot has been opened by a longitudinal curved incision spanning the medial longitudinal arch. The retractor lies beneath a plantar digital nerve.



FIG. 4.—Photomicrograph of a portion of one of the nodules shown in Fig. 3. The more collagenous structure of the normal aponeurosis is seen in the top right hand corner of the field. H. and E.  $\times 55$ .

pieces of evidence he offers in support of the operation of a traumatic factor was the discovery of iron pigment within the nodules, as was identified within the material excised in this case. Such iron was considered to be evidence of small haemorrhages following local lesions of the aponeurosis. In this connexion it is interesting to record that when the patient walked with crutches in the days after operation he complained bitterly of pain in the sole of his unoperated foot; this was found to be the seat of considerable fresh bruising. However attractive this occurrence may be in relation to the traumatic theory of pathogenesis, it must be remarked that no such incident has ever been noted by this patient before.

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#### Trans-Navicular Dislocation of the Carpus.—GEOFFREY R. FISK, F.R.C.S.

Trans-navicular dislocation of the carpus does not seem to have been previously reported, as no references to the condition can be found in the literature.

*Case history.*—B. B., aged 24, a ship's engineer, was found lying unconscious on the railway lines in the London Docks, on September 24, 1952. It was assumed that he had been struck by a passing train, but there seem to have been no witnesses of the accident, so that the exact mechanism of the injury is unknown. He was admitted to the Albert Dock Fracture and Orthopaedic Hospital, where he was found to be suffering from a laceration over the right eyebrow, concussion, and a painful swollen right wrist. X-rays of the wrist revealed a postero-medial trans-navicular dislocation of the carpus, with fractures of the posterior lip of the lower end of the radius, involving the inferior radio-ulnar joint (Fig. 1).

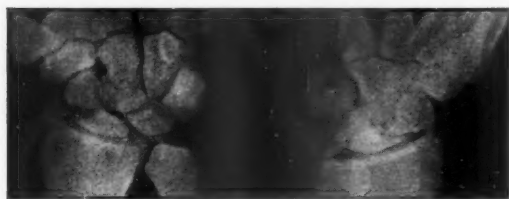


FIG. 1.—24.9.52: Condition on admission.

On September 25, an attempt was made to reduce this fracture-dislocation by manipulation. The carpus was readily replaced on to the lower end of the radius, but there was a tendency for the whole carpus to drift medially at the site of the fracture, and the deformity quickly recurred, even with plaster fixation. A further attempt to reduce the wrist by manipulation was carried out on October 2, without success. Closed reduction was therefore abandoned until the swelling of the wrist had subsided. Open reduction of the fracture and internal fixation, or arthrodesis of the wrist, were considered as the only alternatives. The excision of the proximal fragment of the navicular was not regarded favourably, as this would have destroyed the only intact ligamentous anchorage remaining at the radio-carpal joint. It was thought, however, that excision of the radial styloid might be advisable, in view of the comminuted nature of the fracture and the strong possibility of leaving an irregular articular surface of the navicular after reduction. Open reduction was, therefore, carried out on October 16, 1952, through a "hockey-stick" incision along the lateral aspect of the radius and wrist. The radial styloid was divided and turned distally, carrying the radial collateral ligament. The fractured navicular now came under direct vision, and an attempt was made to reduce this by traction and radial deviation of the hand. Reduction could not be achieved until the hand was strongly pronated, and it immediately became clear that a supination and dorsiflexion force had dislocated the carpus postero-medially, shearing off the navicular through its waist and leaving behind only that part of the proximal pole which was protected by the dorsal radial lip. The proximal fragment had only scanty attachment to its dorsal ligament, so that this fragment had probably been deprived of its blood supply. A fine Kirschner wire was driven into the proximal fragment, and the distal fragment impaled upon it, almost anatomical reduction being achieved (Fig. 2).



FIG. 2.—16.10.52: Position after open reduction.

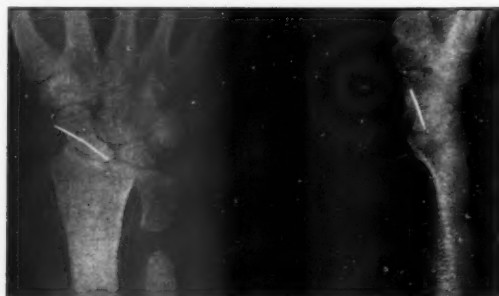


FIG. 3.—1.4.54: Condition at follow-up examination. Showing revascularization of the carpal navicular and the establishment of the pseudarthrosis in the ulna.

The radial collateral ligament was carefully sutured to the periosteum of the radius, and the wrist immobilized in dorsiflexion and radial deviation in a padded plaster cast. As had been expected, avascular necrosis of the proximal fragment occurred, with considerable patchy rarefaction of the bones of the wrist. However, union of the navicular occurred fairly readily. Plaster immobilization was maintained for six months, until revascularization of the proximal pole was present radiologically. The patient then commenced a prolonged course of physiotherapy, in an effort to restore carpal movement, which was largely achieved, but owing to the fracture involving the inferior radio-ulnar joint, rotation remained extremely limited. On August 10, 1953, therefore, excision of 1 cm. of the neck of the ulna was carried out, and by this means rotation of the forearm was fully restored (Fig. 3).

This man was last examined in the Follow-Up Clinic on April 1, 1954. He had given up the sea, and was working full time in his own radio business. He had little pain in the wrist. There was some persistent restriction of volar flexion, but the grip of the hand was excellent and the full range of rotation had been retained.

**Discussion.**—This injury presents several unusual and interesting features. In the first place, the fracture-dislocation could not be fully reduced until the wrist was strongly pronated, showing that this injury was essentially a supination-dorsiflexion injury. Secondly, I have observed on several occasions, on carrying out open reduction or grafting of the ununited navicular, that rotation of the forearm produces a similar rotation at the fracture site, and it may well be that there is often a similar supination element present in the production of this type of fracture, and delayed or non-union is the result of inadequate immobilization. I have come to the conclusion that in most cases of fractures of the carpal navicular, the elbow-joint should be included in the cast.

#### **Bilateral Aseptic Necrosis of the Femoral Heads.**—F. P. FITZGERALD, F.R.C.S.

**History.**—A barman aged 34 complained of aching and stiffness of both hips for six years. He is an epileptic.



FIG. 1.—Bilateral aseptic necrosis of femoral heads. Note symmetry of lesions.

**On examination.**—There was no organic nervous disease. Blood examination was normal. All movements except flexion were absent in both hips: flexion possible up to 90 degrees. X-rays showed aseptic necrosis of both femoral heads (Figs. 1 and 2). The acetabuli were not affected.

The aetiology of the condition is obscure. Obviously there has been a vascular catastrophe in both femoral heads: that both hips should be affected at the same sites and in the same way is unusual. The most probable cause is multiple traumata due to epilepsy. Caisson disease was considered but there was no history of this.

**Treatment.**—All conservative measures failed to relieve symptoms. The left hip was explored and the large dense loosely attached fragment was removed. The site was freshened and as this part of the hip was therefore deficient (Fig. 2) the inside of the cap prosthesis was packed with chips and then fitted in the usual way (Fig. 3). A specimen was removed for examination but the pathological report did not help the diagnosis. A MacMurray type of osteotomy was performed on the other side and fixed with a special plate and nail (Fig. 3).



FIG. 2.—Close up of right side. Head of femur is "squashed". There is a large dense fragment which at operation was found to be loosely attached. The acetabulum is within normal limits.

Eight months after operation the patient is pain-free on the left side; there is a slight ache on the right side, but this is disappearing.



FIG. 3.—Arthroplasty four months ago—painless. Osteotomy two and a half months ago—slight ache. N.B.—The nail is placed low in the femoral neck deliberately in case an arthroplasty should be necessary later.

**Malignant Synovioma.**—M. B. DEVAS, F.R.C.S., and A. D. THOMSON, M.R.C.P.

*Introduction.*—In the literature there are reports of 204 cases of malignant synoviomata (Haagensen and Stout, 1944; Bennett, 1947; King, 1952; and Wright, 1952). The comparative rarity of this tumour prompted us to show these 3 recent cases which were all in the wards of the Middlesex Hospital at the same time.

*Case I.*—G. H., female, aged 43.

June 17, 1954: Admitted with a three-weeks history of swelling of the right thigh in the supra-patellar region. The patient is positive that there was no swelling previously. The



FIG. 1 (Case I).—Showing a cystic and haemorrhagic tumour arising from the supra-patellar pouch and invading the thigh.

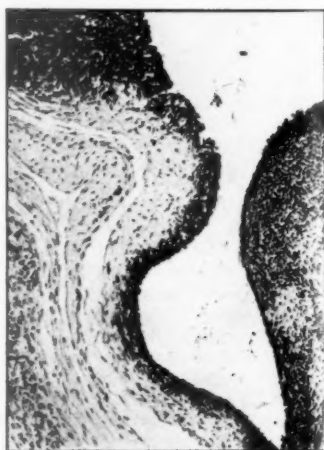


FIG. 2 (Case I).—Showing the synovial membrane of the supra-patellar pouch and the transition to tumour.  $\times 65$ .

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swelling was the size of a grapefruit, occupied the region of the supra-patellar pouch and was tense and fluctuant. X-rays showed no abnormality of the bones.

June 18, 1954: *Biopsy*. The swelling consisted of thickened synovia of the supra-patellar pouch and contained clear fluid with white flakes. There was no connexion with the knee-joint but in one area there was a thick nubbin of synovia.

*Operation*—July 1, 1954 (Mr. Philip Wiles).—Disarticulation of the hip.

September 10, 1954: The patient was discharged.

The amputation specimen showed a hæmorrhagic and partially cystic tumour arising from the supra-patellar pouch and invading the muscles of the thigh (Fig. 1).

Fig. 2 shows the tumour arising from the synovial cells of the supra-patellar pouch. Microscopically the tumour is composed of a mass of undifferentiated spindle cells in which mitoses are numerous (Fig. 3).

Histologically, there was no evidence of invasion of blood vessels or lymph nodes.

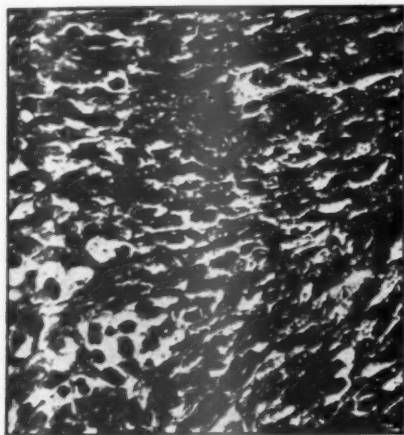


FIG. 3. (Case I).—Showing the cellular undifferentiated spindle cell synovioma with mitoses.  $\times 400$ .



FIG. 4 (Case II).—Showing the swelling of the left buttock.

*Case II.*—T. D., male, aged 63.

June 1953: Onset of pain in the left hip. At first treated as fibrositis. He was referred to his local hospital in November 1953. Physiotherapy was instituted.

March 1954: A lactic acid injection was given. A swelling then appeared in the left buttock.

May 1954: A biopsy was performed and the histology suggested a spheroidal-cell carcinoma, perhaps coming from the prostate.

June 1954: Admitted to the Middlesex Hospital. There was a large tumour of the left buttock (Fig. 4). The X-ray showed slight erosion of bone most marked in the femoral neck (Fig. 5). Deep X-ray therapy was started.

June 14, 1954: *Examination under anaesthesia*. The tumour was found to enter the pelvis from the buttock and appeared to merge into the prostate on bimanual examination. A portion of tumour was taken for histological examination. The condition of the patient gradually deteriorated, and on August 9, 1954, he died.

The specimen removed at autopsy, showed a firm pale tumour arising from the hip-joint and invading the soft tissues. The tumour had extended to invade the neck of the femur and the acetabulum with extension of the tumour into the pelvis through the obturator foramen (Fig. 6).

Microscopically, the tumour is composed of polyhedral cells in a hyaline stroma (Fig. 7). In areas there is some differentiation of the tumour cells with the formation of clefts (Fig. 8).

Post-mortem revealed that the tumour had metastasized to the liver, which was almost entirely replaced by growth, and weighed 190 oz. (normal 50–60 oz.).



FIG. 5 (Case II).—Showing the area of bone erosion of the neck of the left femur.



FIG. 6 (Case II).—Showing the tumour mass arising from the synovial membrane of the hip and involving the femoral neck. The tumour has extended through the obturator foramen into the pelvis.

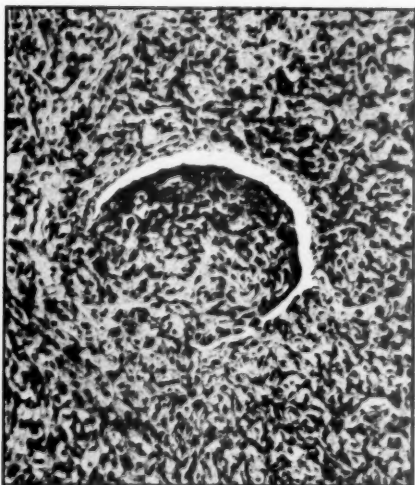


FIG. 7 (Case II).—Showing the cellularity of the tumour.  $\times 100$ .

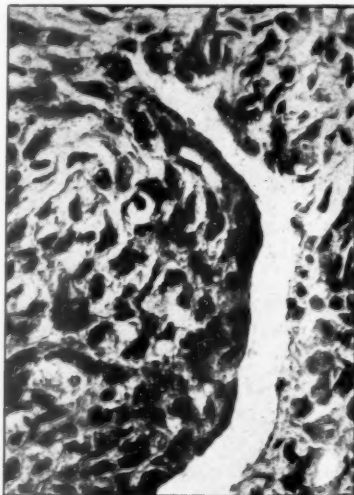


FIG. 8 (Case II).—Showing cleft formation in the tumour indicative of some differentiation of the tumour cells.  $\times 285$ .

**Case III.**—R. R., male, aged 47.

January 1954: Onset of stiffness in the right hip. Shortly after this aching occurred in the right knee. This was followed by swelling in the right upper thigh and around the hip.

June 1954: The patient was admitted. He was found to have a large swelling over the right thigh and hip and considerable limitation of movement at the joint (Fig. 9). The X-ray showed cystic destruction of the femoral head and neck of the acetabular region (Fig. 10).

June 10, 1954: *Biopsy.* The synovial membrane of the hip was thick and dark brown and

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FIG. 9 (Case III).—Showing the swelling of the right hip region.



FIG. 10 (Case III).—Showing the X-ray with cystic destruction of the femoral neck and acetabulum.



FIG. 11 (Case III).—Showing the variegated tumour in the femur, acetabulum and soft tissues. (Compare with X-ray appearances.)

there was an excess of thick brown fluid in the joint. Bone and synovia were sent for section. July 10, 1954 (Mr. Wiles): Hindquarter amputation. The patient made an uneventful recovery and was discharged on August 10, 1954.

The hind-quarter amputation specimen showed red- and brown-coloured tumour invading the femoral neck, the acetabulum and the soft tissues (Fig. 11).

Microscopically the tumour in the soft tissue and bone is composed of malignant synovial cells with many giant-cell forms in which phagocytic cells containing brown-coloured granules of hemosiderin are seen (Figs. 12 and 13).

Histologically there was no evidence of invasion of blood vessels but the pelvic group of lymph nodes were invaded by tumour tissue identical in appearance to the primary growth.

**Comment.**—These 3 cases presented with pain, stiffness or swelling and the true nature of the condition was only diagnosed after extensive biopsy. The first case (G. H.) shows a completely undifferentiated spindle cell tumour; the second case (T. D.) shows some histological differentiation of the tumour cells with cleft formation and the third case (R. R.) is an example of the rare malignant giant cell synovioma.

Mr. Devas said, in reply to the President, that he had looked up the recorded cases of malignant synoviomata and that he had only found 5 said to have arisen from the hip in over 200 cases. However, there were 7 cases described as presenting in the groin or buttock. The knee and adjacent structures were a much more common site.

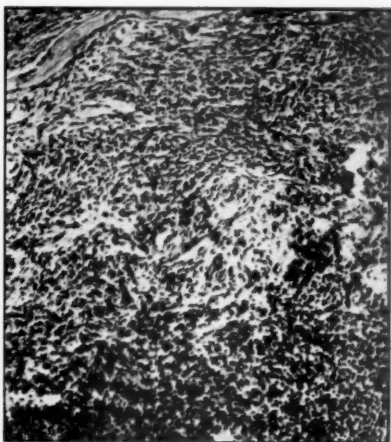


FIG. 12 (Case III).—Showing a cellular synovial tumour with some giant cells.  $\times 75$ .

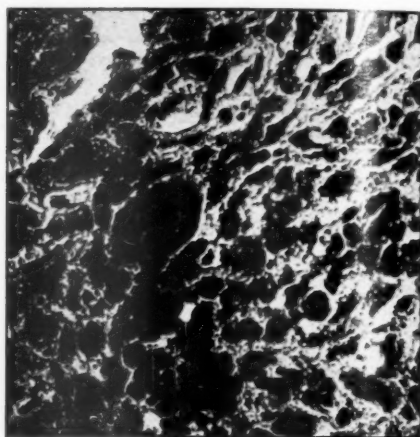


FIG. 13 (Case III).—Showing the malignant synovial cells with giant cell forms and granules of haemosiderin in the tumour tissue.  $\times 400$ .

#### ACKNOWLEDGMENTS

We wish to thank Mr. Philip Wiles (Case I), Miss M. D. Snelling (Case II) and Mr. P. H. Newman (Case III) for permission to show these cases. We are also indebted to Dr. W. W. Richardson for the autopsy findings on Case II.

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Mr. G. R. Fisk said that he had seen 3 cases of pigmented villo-nodular synovitis, in which the clinical and histological features closely resembled the third case shown by Mr. Devas. These 3 cases all showed invasion of surrounding soft tissues and bone by granulomatous material. It seemed to be a very difficult problem to differentiate between the condition of synovioma, which was highly malignant, and another which was patently benign.

The following cases were also shown:

**A Bony Mass Anterior to the Hip Joint Following Long-standing Paraplegia with Successful Resection.**—Mr. K. I. NISSEN. (Previously shown October 6, 1953, see "Proceedings", 1954, 47, p. 15, Case III, Mr. J. C. McNEUR.)

**Tibia Vara.**—Mr. J. W. DICKSON (for Mr. P. H. NEWMAN).

**Arthroplasty of the Elbow in Rheumatoid Arthritis.**—Mr. R. C. F. CATTERALL.

(1) Albright's Disease. (2) Polycystic Fibrous Dysplasia.—Mr. H. A. KIDD.

**Giant Cell Tumour of the Right Femoral Head.**—Mr. R. H. SEWELL.

**A New Method of Arthrodesis of Ankle and Elbow in Quiescent Tuberculosis.**—Mr. A. C. BINGOLD.

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## Section of Dermatology

President—REGINALD T. BRAIN, M.D., F.R.C.P.

[October 21, 1954]

**Miescher's Granulomatosis with Mediastinal Gland Enlargement.**—R. J. CAIRNS, M.B., M.R.C.P.

Mr. F. J. S., aged 61.

**History.**—Abrasions to both shins twenty-five years ago were followed by the appearance of scaly plaques. These have persisted, the original patches slowly enlarging and new lesions appearing on the backs of the calves and around the knees. Two years ago a violaceous disc appeared on the back of the right forearm and about one year ago lesions appeared on the lumbar region.

**Previous history.**—Not relevant.

**Family history.**—No family history of diabetes. No tuberculosis.

**On examination.**—Over the middle third of both shins are large plaque-like areas with a violaceous, infiltrated margin, varying from 2 to 7 mm. in width. The centre is waxy and yellowish with telangiectatic vessels showing through the atrophic epidermis and in parts there are rather silvery scales. On the right wrist is an oval patch  $1\frac{1}{2}$  cm.  $\times$  1 cm. It has a scaly, slightly violaceous margin and a clear, atrophic centre. Over the left scapula is a large, irregular patch with a violaceous, slightly infiltrated margin with no scaling. The centre of the patch is not atrophic. On the sacral region are two violaceous, infiltrated patches and there are similar scattered plaques on the right loin as well as on the right forearm.

Abdomen normal. C.V.S. normal. B.P. 160/110.

**Investigations.**—X-ray of chest: Bronchitis and emphysema. Screening of chest: There is a glandular mediastinal shadow and some splaying of the tracheal bifurcation, probably also due to enlarged glands. This swelling appears to be too high to be the left auricle. X-ray of hands: No sarcoid changes demonstrated. Blood count normal. Serum proteins: Total 7.6%; albumin 4%; globulin 3%; fibrinogen 0.6%. B.S.R.: 20 mm. in one hour (Westergren). Serum calcium 10.5, cholesterol 236 mg.%. Mantoux negative 1 in 100. W.R. and Kahn negative. Blood sugar and sugar tolerance normal.

**Skin biopsy.**—The epidermis is normal. Within the dermis is a dense granuloma extending from below the papillary zone to the border of the subcutis. Sweat gland elements and pilar follicles and muscles are preserved within the area. The granuloma consists of foci of lymphocytes, monocytes and a large number of multinucleate giant cells. The collagen and blood vessels appear normal and reticulin fibrils permeate the foci. No fat, iron or acid-fast bacilli were demonstrated.

A section of an earlier plaque shows an essentially similar picture with rather more discrete granulomatous foci within the dermis.

**Comment.**—The relation of this granulomatosis to lipoid necrobiosis still remains in doubt. There is a possibility that this dermal granuloma is a variant of sarcoidosis of the skin or alternatively that it is primarily a vascular reaction with secondary granulomatosis. Tappeiner (1952) thought that it began in the vascular adventitia. Another alternative seems to be that it is a benign reticular hyperplasia comparable to Stengel-Wolbach sclerosis (giant-celled histiocytic reticulosis). Certainly this case shows more resemblances histologically to this reticulosis than to sarcoidosis. Stengel-Wolbach sclerosis is most commonly seen in the spleen and resembles a diffuse granulomatous tuberculosis (Robb-Smith, 1938). Reticulin and collagen fibrils run in between the cells as well as encircling the nodule but necrobiosis has never been observed.

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**Dr. P. J. Hare:** I would accept the diagnosis but I do not think that granulomatosis disciformis is a pathological entity. One case has been attributed to tuberculosis and successfully treated with streptomycin, &c., whilst others have been reasonably thought to be due to sarcoid, and yet others may have been caused by foreign body reactions. The mere name does not seem to assist very much in understanding these cases.

M.R.

**A Rare Variety of Squamous cell Carcinoma.**—E. J. MOYNAHAN, M.R.C.P.

A man aged 79, retired, who noticed two small lumps on his right upper eyelid about six years ago. These slowly increased in size and coalesced and at that time were brownish in colour. Last year the lesion increased rapidly in size to its present dimensions and about two months ago it became infected. The infection was cleared by treatment with aureomycin and there now remains a well-circumscribed lesion involving the skin of the lower part of the upper eyelid, but not invading the palpebral conjunctiva. The lesion is indurated, lobulated, and ulcerated in several places (Fig. 1).



FIG. 1.

The histology reported on by Dr. Haber reveals a keratinizing squamous cell carcinoma of an unusual variety.

**Dr. H. Haber:** The epidermis looks normal. The corium is entirely replaced by masses of cells, which quite distinctly derive their origin from the epidermis. They "segregate" at the epidermodermal junction as seen in junctional naevi, malignant lentigo or melanomas. In clear distinction to melanoma cells these cells show a tendency to cornification. In several places one can detect prickles. The tumour shows very marked pleomorphism, the cells exhibiting different stages of cornification with bizarre-looking nuclei, pyknosis and vacuolation. Some cells have undergone complete hyalinization with loss of nuclei. This is an unusual type of a highly differentiated squamous cell epithelioma (Figs. 2 and 3).

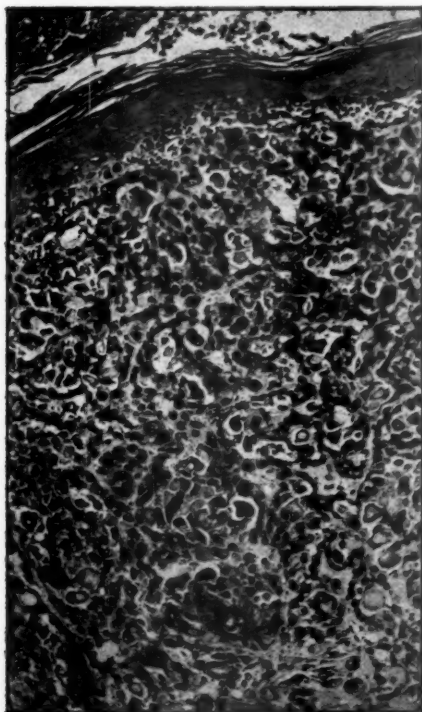


FIG. 2.—H. and E.  $\times 215$ .

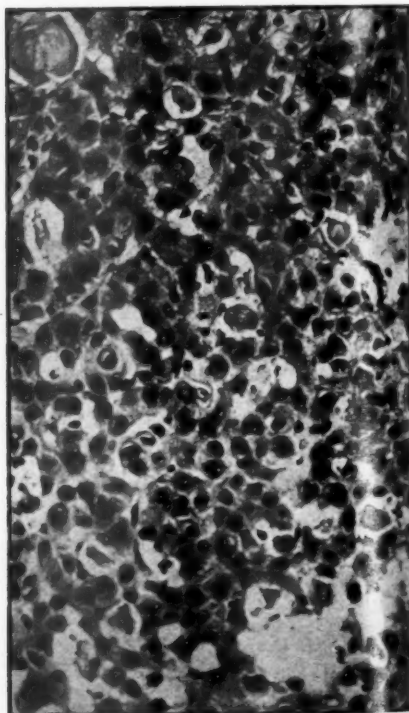


FIG. 3.—H. and E.  $\times 585$ .

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**Fungus Infection.**—R. H. MEARA, M.B., M.R.C.P.

D.C., schoolboy, aged 6.

**History.**—When 3 weeks old he developed a universal scaly erythematous eruption which was diagnosed as erythroderma desquamativum (Leiner). The condition gradually cleared in the first year of life but left some scurfiness of the scalp, around the eyes and on the face. The child continued to have some slight scaliness on the trunk and limbs at times but four months ago a scaly red eruption appeared on the lower limbs with vesicles on the palms and soles. The rash has varied in intensity and outline since then.

**On examination.**—On the legs and buttocks are ill-defined, scaly, erythematous areas. Scaling of the palms and soles is also present together with dry scaling spots which suggest dried up vesicles. The toe webs show considerable scaling and peeling. There is also considerable scurfiness of the scalp, with some scaling of the outer angles of the eyelids and a few patches of pityriasis alba of the face.

**Investigations.**—Direct examination for fungus: Hands, feet and legs: Fungus present; scalp and face: No fungus found. Culture: *Epidermophyton floccosum* grown from the feet, legs and hands.

**Comment.**—This type of widespread fungus infection due to *Epidermophyton floccosum* is occasionally encountered although it is much more commonly due to *Trichophyton rubrum* infection. It is, however, very unexpected to find this kind of infection in a lad of 6 years. No fungus infection could be found in any of the members of the patient's family.

I wish to thank Dr. R. T. Brain for kindly allowing me to publish this case.

**Addendum (5.12.54).**—After four weeks' treatment with Whitfield's ointment the eruption had healed except for some residual scaling of the palms and soles. On microscopical examination, fungus was found only in these areas.

The following cases were also shown:

**Psoriasis and Lupus Erythematosus.**—Dr. F. P. HALL-SMITH.

**Favus (Two Cases).**—Dr. P. J. FEENEY.

**Phagedena Geometricum (Brocq)** (Case History Only and Illustrations).—Dr. P. J. HARE. [This case will be published in the *Proceedings of the St. John's Hospital Dermatological Society*.]

**Poikiloderma Atrophicum Vascular.**—Dr. C. D. CALNAN.

**Orf.**—Dr. E. N. M. JOHNSTON (for Dr. E. W. PROSSER THOMAS).

[November 18, 1954]

**Berylliosis.**—I. B. SNEDDON, M.B., M.R.C.P.

F. W., aged 25. Shearing machine operator.

This girl was referred for treatment in August 1954. She stated that she had cut her left foot at work in May 1954 and the cut had never healed.

**Past history.**—Raynaud's phenomenon and arthritis of the fingers of the right hand at age of 10.

**Family history.**—Not significant.

**On examination** (August 1954).—She showed cold, blue fingers and some old arthritic change in the fingers of the right hand.

On the fronts and backs of the fingers and in the palms were numerous firm, non-tender nodules, a few of which showed superficial ulceration; up the forearms were several scratch marks which showed a papular granulomatous eruption along the scratches. Similar lesions were present on the legs. On the top of her left foot was a granulating ragged ulcer, on the site of the cut, 1 in.  $\times$   $\frac{3}{4}$  in.

**Occupational history.**—She has been employed by a smelting company for eight and a half years. For the first five years she was employed in the rolling mill and for the last three and a half years she has worked a rotary shearing machine trimming strip metal, a fair amount of which has been 2% beryllium copper. The sharp edges of the metal strips frequently cut her hands, forearms and legs. It was the beryllium copper strip which cut her foot and which was responsible for some of the scratches on her legs, arms and hands. She has never been exposed to any silica dusts.

**Investigations.**—A section of the skin from the left middle finger shows marked hyperkeratosis over the surface. In the dermis are numerous well-circumscribed nodules separated by dense, fibrous tissue. The nodules consist of foci of epithelioid cells, multinucleated

giant cells and small round cells. There is no caseation in the centre. The appearances are suggestive of Boeck's sarcoid but they might possibly be due to a foreign-body reaction to beryllium.

Dark ground and polarized light examination of the section shows no foreign bodies. Mantoux tests: 1/1,000 and 1/100 negative. Blood W.R. and Kahn negative. Blood count: Hb 96% (14.2 grams/100 ml.); M.C.D. 7.2 $\mu$ ; W.B.C. 6,000 (neutros. 60%, eosinos. 2%, lymphos. 30%, monos. 8%). Red and white cells normal.

Plasma proteins: Total serum proteins 7.3; albumin 4.8; globulin 2.5 grams/100 ml. X-rays: Chest (6.9.54): Diaphragm normal. Heart not enlarged. Lungs show very fine reticular pattern and the appearances are consistent with sarcoidosis.

15.11.54: The appearances of the lung fields are unchanged. They consist of generalized very fine stippling overlying the otherwise normal lung.

Reconsideration of these films indicates that the picture is not the usual one seen in sarcoidosis where the stippling is usually a little denser and the hilar glands are commonly involved. The evidence, therefore, seems to point to these changes being berylliosis rather than sarcoidosis, although, of course, the distinction is extremely difficult.

Hands and feet: No evidence of bony lesion.

Miniature radiographs of the chest taken in October 1953 and August 1954 do not demonstrate changes.

Estimation of beryllium in twenty-four-hour urine: negative.

Estimation of beryllium in skin containing granulomatous papules: negative.

Patch tests:

2% beryllium sulphate	+++	2% beryllium nitrate	+++
1% beryllium sulphate	++	1% beryllium nitrate	++

**Progress.**—During the last two months the patient has developed dyspnoea on exertion and a cough.

Granulomatous papules have been observed to develop in scratches due to beryllium copper and a granulomatous nodular lesion has appeared in the ulcer on her left foot.

**Comment.**—Recent criteria for the diagnosis of berylliosis suggested by DeNardi *et al.* (1953) were: (1) History of exposure to beryllium. (2) Clinical course. (3) X-ray evidence of granulomatosis of lung. (4) Lung biopsy and analyses for beryllium. (5) Patch tests.

How does the present case measure up to these criteria?

(1) She is exposed to 2% beryllium copper; not usually considered to be a hazard. It is used a great deal in the electrical industry. Her job is really a clean one; she is exposed to minute particles of the beryllium copper though there is negligible dust in her workshop and she does cut herself with the sharp edges of the strips. I think we can rule out her five years in the rolling mill as there was no beryllium being used at that time.

There is a precedent for beryllium copper as a hazard. In an American industrial concern (Jackson, 1950), 6 out of 300 workers developed delayed chemical pneumonitis and they had had no more contact with beryllium than this girl.

(2) The skin lesions are typical of sarcoid-like granuloma which has previously been described. They are very like Lederer and Savage's case (1954) and she has also shown ulcers like chronic beryllium ulcers.

(3) The course of her illness is rapidly progressive. Her dyspnoea has become worse in the last month.

(4) The X-ray changes are typical of the early stages as described by Wilson (1948).

(5) The patch tests to 1 and 2% beryllium salts were markedly positive and the control subjects showed no response.

There are no positive evidences of sarcoidosis such as bone changes or a raised blood globulin, both of which are absent in berylliosis.

The Mantoux is negative in both conditions.

**POSTSCRIPT.**—A skin biopsy taken from the site of the beryllium nitrate patch test three weeks afterwards showed a typical sarcoid-like reaction in the dermis.

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**Dr. F. F. Hellier:** As to the significance of a negative Mantoux test, I would like to draw attention to a recent article by Hoyle *et al.* (1954) who showed that depression of the reaction might be found in any disease involving the reticulo-endothelial system such as

Hodgkin's disease. Dr. R. patch test to become the patient's Dr. H. sensitized but she she was lungs do to speculate inhaling Dr. C. nickel-se on the h their sus positive. Dr. R. easily th Dr. V. contact v Dr. F. of reacti patients? alteration Dr. S. have been pneumon the disea may expl It is kn show ep I have work wit workers risk. Dr. H. or does h Dr. S. its radiol lymph gl clinically diagnosis

Dr. F. F. Hellier: As to the significance of a negative Mantoux test, I would like to draw attention to a recent article by Hoyle *et al.* (1954) who showed that depression of the reaction might be found in any disease involving the reticulo-endothelial system such as

Hodgkin's disease and other conditions quite unrelated to sarcoidosis. It is thus a non-specific change due to the site of the disease and not to its specific character. As Dr. Sneddon has said, the prognosis in berylliosis is bad and we must ask ourselves how we can remove the beryllium from this girl's system. I understand B.A.L. has been tried in berylliosis without success. I would suggest investigating the possibility of using a chelating agent. These are substances which form inert compounds with certain metals and have been used in treating lead poisoning. I do not know whether one can be found which will extract beryllium but I feel the possibility should be explored as it seems the only hope for this girl.

## REFERENCE

HOYLE, C., DAWSON, J., and MATHER, G. (1954) *Lancet*, ii, 164.

**Dr. R. D. Sweet:** I would like to comment on Dr. Sneddon's question about the positive patch test. From what he says it is usual for a person constantly in contact with beryllium to become epidermally sensitized to it. It may be that from handling the beryllium copper the patient has become sensitized, although this might not be related to her sarcoidosis.

**Dr. H. R. Vickers:** This is a very fascinating case. If the patient had been epidermally sensitized previously one would have expected to get an eczematous outbreak on her hands but she has developed this sarcoid-like lesion and ulcers and no epidermal sensitivity until she was patch-tested—which seems a little peculiar. She demonstrates very well that the lungs do take part in the sensitivity reaction test as we see it in the skin. It is also interesting to speculate how the beryllium has got into the lung tissue. There is no obvious risk of inhaling beryllium. Perhaps it has been absorbed through the skin.

**Dr. C. D. Calnan:** Dr. Vickers's point about the metal sensitivity may not be valid. Many nickel-sensitive women handling knives, forks, spoons and similar articles get no trouble on the hands and quite a number may be able to return to using metal suspenders after their suspender dermatitis has subsided, even though the patch test to a nickel salt remains positive.

**Dr. R. D. Sweet:** A soluble salt, in solution, may evoke a reaction much more quickly and easily than the insoluble metal itself when applied to the skin.

**Dr. Vickers:** This girl must have a sensitive skin to get a sarcoid reaction; it is not casual contact with coins or other metal; the contact is ever present.

**Dr. F. Ray Bettley:** These people with negative Mantoux seem to have a peculiar state of reactivity or non-reactivity of the skin. Have Kveim tests been done on berylliosis patients? If not perhaps one could be carried out on this patient. One suspects some alteration in the general reactivity.

**Dr. Sneddon:** I think I can throw a little light on some of these points. The Kveim tests have been done on American cases and have been negative. The only other case of beryllium pneumonitis reported in this country had a positive Mantoux which became negative after the disease had progressed for some time. Beryllium metal is extremely insoluble and this may explain why the patient had no contact dermatitis, when handling the alloy.

It is known that all the cases of chronic berylliosis of the lung which have been tested show epidermal sensitivity.

I have looked at some of the other workers and they do not get sarcoid lesions when they work with beryllium copper. I think the next thing will be to patch test some of the other workers. There is a little risk that one might sensitize them but perhaps we might take this risk.

**Dr. H. J. Wallace:** Does Dr. Sneddon regard this as an entity quite apart from sarcoidosis or does he regard it as sarcoidosis precipitated by the metal?

**Dr. Sneddon:** It is a completely distinct entity from sarcoidosis, it has distinct features, its radiological appearance is different, its pathology is different, it never affects bones or lymph glands, except those draining the lungs. It can be differentiated from sarcoid but clinically it is difficult to do so; the fact that there is a positive patch test gives the differential diagnosis.

**Dermatitis Herpetiformis (Erythemato-squamous type).—I. B. SNEDDON, M.B., M.R.C.P.**

H. H., aged 68. Retired clerk.

Since 1947 he has suffered from recurrent attacks of an irritable vesicopustular eruption. The rash started on his chest and extended to the axillæ and groins and attacks have mainly affected those areas since. Severe outbreaks of the eruption occur about every three months and gradually die away in three to four weeks though he is never completely free from lesions.

Since June 1954 the eruption has been more severe than ever before and the itching more intense. Apart from the rash he enjoys good health. He takes no drugs.

*Past history.*—Rheumatic fever when 21 and prostatectomy when 60.

*Family history.*—Not significant.

*On examination.*—The skin eruption has been observed since 1947 and consists of a primary vesicopustule which extends into a serpiginous scaling and crusted lesion with central clearing. The face and mouth have always been spared and the axillæ and groins have been mainly affected. Slight pigmentation is left when the lesions heal.

*Investigations.*—Biopsy: A section of the biopsy taken from the skin of the axilla shows the raising up of a small septic blister in the epidermis. The superficial covering of this blister is formed by the horny layer only, while its base is formed by the granular layer. Numerous polymorphs are present in the blister and they can be seen extending down a hair follicle in the floor of the blister. Numerous apocrine glands are present in the corium. A few scattered polymorphs are present in the dermis with some small round cells. The appearance is not typical of dermatitis herpetiformis but is more in keeping with a small septic blister as seen in impetigo contagiosa.

Culture (aerobic and anaerobic): Yielded a heavy growth of a *Staph. pyogenes*.

Blood count: Hæmoglobin 97%; W.B.C. 6,000 (neutros. 72%, eosinos. 3%, lymphos. 19%, monos. 6%).

Urine examination—no abnormality.

During the years since 1947 many different forms of treatment have been tried. Antibiotics including penicillin and aureomycin have been valueless.

Sulphapyridine was not tolerated and Sulphamezathine was of no value. He was given Fowler's solution 5 minims t.d.s from 29.7.54 until 14.8.54 and the eruption cleared. It relapsed within three days and again cleared with liquor arsenicalis until on 15.9.54 diamino-diphenylsulphone (D.D.S.) 50 mg. t.d.s. was substituted and the eruption remained clear and was clear on 30.10.54. Since then he has had no treatment and the eruption has recurred.

*Comment.*—This case resembles closely the 2 cases shown here by Dr. Wilkinson in 1951 under the diagnosis of chronic vesicular impetigo. All have in common the long history of recurrent attacks of superficial vesicopustules which develop into annular and serpiginous shapes. The lesions affect particularly the axillæ and groins. All have shown the distinct subcorneal blister filled with polymorphs and though in this case *Staph. aureus* was found, and in one of Wilkinson's *Staph. albus* was present, antibacterial treatment has failed to control the eruption.

This patient's eruption has, however, been controlled with Fowler's solution and D.D.S. and cessation of treatment has been followed by immediate relapse.

The condition differs completely from the classical impetigo herpetiformis of Hebra which is a severe disease almost always occurring in pregnant women. The only references to similar eruptions I have been able to trace are a case described by Gougerot *et al.* in 1935 which they called "formes érythémato-squameuses, 'atipiques' de la dermatite polymorphe de Brocq-Duhring". They described a case in a man aged 22 who had had an eruption of the same type which came in attacks three times yearly, the first attack being seven days after birth. Tzank (1948) in his article on the immediate cytologic diagnosis in dermatology shows a diagram of a subcorneal blister in dermatitis herpetiformis but makes no other reference to it.

In 1954 Anthony Cipollaro showed a case at the New York Society of Dermatology, with a serpiginous vesicopustular eruption of two and a half years' duration in the groins and axillæ in a man of 51. The blister was intra-epidermal and the consensus of opinion was that it was an atypical dermatitis herpetiformis.

I believe that that is as near as one can get to a diagnosis at present, though it undoubtedly differs from the classical clinical picture of dermatitis herpetiformis and may be a specific entity.

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 WILKINSON, D. S. (1951) *Proc. R. Soc. Med.*, 44, 241; *Brit. J. Derm.*, 63, 326.

**Dr. D. S. Wilkinson:** I am sure this is exactly the same condition as in my cases; the characteristics seem to be the site, radiating from the axilla and groin, the superficial nature of the eruption and its comparative failure to respond to sulphapyridine (although it may

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respond partially). Both my cases did this. We painted them with thorium X after the Section meeting and there had been no further activity. The reason for this I do not know, but it is another feature which distinguishes it from typical dermatitis herpetiformis.

**Dr. P. J. Hare:** This case reminds me of a condition described by Crawford in 1949 as "chronic symmetric impetigo". We have had 2 cases similar to this, one in a boy of 8 and the other in a nurse. In the boy's case we at first entertained the notion of dermatitis herpetiformis but in both cases the histology was that of impetigo with a subcorneal accumulation of polymorphs. The reaction to antiseptic treatment was disappointing but the boy's lesions were suppressed by continuous treatment with Steroxin ointment.

#### REFERENCE

CRAWFORD, S. (1949) *Arch. Derm. Syph., Chicago*, **59**, 55.

**Dr. J. R. Simpson:** I showed here in 1948 a man with an eruption similar to this (*Proceedings*, **41**, 307). I was told that it was dermatitis herpetiformis and that I should give him more arsenic which I did without any effect whatever. I was delighted when Dr. Wilkinson showed his cases, and tried thorium X on mine; it did him good. I am pleased to find other people agree that there is a difference between this condition and the ordinary type of dermatitis herpetiformis.

**Dr. J. Ferguson Smith:** I have seen this type of eruption apparently due to a mixture containing iodine, given for asthma. Might not a single finding of a bulla or pustule in an unexpectedly superficial situation be due to a secondary infection?

**Dr. H. Haber:** All cases show the same characteristic histology: a strictly subcorneal bulla containing masses of neutrophils and no organisms. It resembles the histological appearance of impetigo contagiosa. This condition seems to be an entity.

#### Diffuse Pigmentation in Brothers.—J. S. PEGUM, M.D., M.R.C.P.

I.—A. W., aged 7 years 8 months.

**Histology.**—At birth the patient was of normal colour. At 4 months there was a gradual onset of brown pigmentation, commencing in the external genitalia and in the groins and spreading up over the trunk to the neck. At 1 year white patches were noticed by the mother in the groin region; these have persisted. The pigmentation became gradually darker and reached its maximum at the age of 5 years. In the past few months it has started to lessen. There has been no seasonal or diurnal fluctuation in the degree of coloration.

**General health.**—The boy has always been slight of build and has never been robust. His appetite declined as his pigmentation increased and now is increasing as his pigmentation declines. He has always been fond of fats, milk and butter.

**Previous illnesses.**—He was in hospital from the age of 1 year to 15 months with muscular weakness and a hunched back from both of which he recovered. While in hospital he suffered from bilateral mastoiditis and from gastro-enteritis.

**Family history.**—Father: English, light brown hair, fair skin. Mother: English, brown hair, brown eyes, fair skin. Grandparents and great-grandparents: all white-skinned. Younger brother has started to pigment (*see below*). Parents unrelated.

**On examination.**—He is a thin boy of slight build with brown hair and brown eyes. The face is olive and the trunk dark brown, almost negroidal in hue. The thighs are also dark, shading to a lighter shade in the lower legs. There are numerous white speckles all over the trunk and groins, size 1–5 mm. in diameter. There is keratosis pilaris on the trunk. The arms are pigmented but less than the trunk; the palms and soles are slightly pigmented. The axillae are pale, the nipples quite black. There are small patches of brown pigment on the tongue and buccal mucosa, and there is a band of pigmentation along the gums. The testes are undescended. The chest, the abdomen, the C.N.S. and C.V.S. are all normal. The blood pressure is 120/80.

**Investigations.**—X-rays chest, abdomen and skull normal.

Blood count: Haemoglobin 74%; white cells 11,200 (polys. 55%, lymphos. 42%, monos. 3%).

Blood chemistry: Chlorides 610, serum sodium 346, serum potassium 21.5 mg./100 ml.

Total plasma protein 7.1, albumin 5.2, globulin 1.9 grams/100 ml.

Kopler index: 29 (normal).

Urine: Urobilinogen present within normal limits. No bilirubin detected. No melanin or other abnormal pigments seen. Fat balance test: total intake 200 grams, fat absorbed 87%.

Biopsy from skin of abdomen: Epidermis: normal except that there is an increase in pigmentation in the basal layer and in the rete malpighii. Dermis: normal but upper dermis shows dark brown blobs of pigment intracellular and extracellular.

II.—G. W., aged 2 years 5 months.

*History.*—At birth the patient was of normal white colour. Between 1 year and 20 months pigmentation began on the abdomen and neck. General health good. As his skin has grown darker his appetite has declined. Like his brother he likes fatty foods.

*On examination.*—Well-built little boy with fair hair and blue eyes. The lower chest, the abdomen and the back are distinctly tan-brown in colour. The axillæ are darker brown and the nipples dark brown. Palms and soles are slightly pigmented. Mouth shows no sign of pigmentation. Blood pressure 100/50. Testes normal.

*Comment.*—These brothers present a most unusual clinical picture and the diagnosis presents corresponding difficulties. Racial pigmentation is, I suppose, the first thing to exclude. It seems unlikely since there is no family history of coloured skin and pigmentation did not begin at birth. The histology is also against this explanation since in the dark races the pigment is most marked in the basal cell layer of the epidermis and is then shed outwards, whereas in the older of these two boys, while there is much pigment in the basal cell layer a good deal appears to have been shed inwards into the dermis as in incontinentia pigmenti. Addison's disease is not supported by the investigations carried out on the older boy or by any decline in general health of appropriate magnitude. There is little to support the diagnosis of hæmochromatosis, argyria, chrysiasis or sprue. The histology is similar to that of incontinentia pigmenti but the clinical history and examination do not support this diagnosis. Wende and Bauckus (1919) described a very similar condition in a brother and sister born in the U.S.A. of White Russian parents. This was diffuse pigmentation commencing in both cases at the age of 1 year and fading in the older at 5. The similarities and differences between their cases and mine are as follows:

Age of onset: Both their cases began at the age of 1 year. One of my cases began at 1 year, the other at 4 months.

Sex: Their cases were brother and sister; the present cases are brothers.

Pigmentation: Pigmentation in all four cases was diffuse. In one case in each pair there were white macules. Pigmentation was similar in hue and intensity. Mode of spread was a little different since in Wende and Bauckus' cases pigmentation began in the scalp and spread down whereas in my cases it began in the groins and trunk and spread both up and down. The mouth is affected in one of my cases but in neither of theirs. They emphasize the zonal nature of the pigmentation in one of their cases and there is slight zonal effect in the older brother of my pair. Wende and Bauckus describe variation in colour with light of the chameleon type in one of their cases: the boy was said to become paler on exposure to light and darker in the dark. Neither we nor the mother have been able to observe this phenomenon in these patients: further, an injection of 25 mg. ACTH was given to the elder and photos taken under identical lighting conditions before and after to see whether the intermedin, which contaminates ACTH, produced darkening. It did not.

Muscular weakness: There is a history of muscular weakness in one of my cases and in one of theirs.

Histology was similar.

Summing up, one is inclined to label these cases diffuse pigmentation of the Wende and Bauckus type. The mechanism of the pigmentation is not clear. Cockayne (1933) suggested it was due to a recessive gene.

The pigmentation in the elder boy is fading and if Wende and Bauckus' case is any guide should continue to do so. If the smaller boy's coloration increases we could try the effect of cortisone to see if it has the effect which it has in Addison's disease.

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WENDE, G., and BAUCKUS, H. (1919) *J. cutan. Dis.*, **37**, 685.

The following cases were also shown:

**Nodular Dermal Allergide (Trisymptome de Gougerot).**—Dr. C. D. CALNAN.

**Nodular Dermal Allergide (Gougerot).**—Dr. G. A. BECK.

**Two Cases of Cutaneous Allergic Arteriolitis.**—Dr. H. HABER and Dr. HAROLD WILSON.

**Three Cases of Onychomycosis Caused by *Scopulariopsis brevicaulis*.**—Dr. R. J. CAIRNS and Dr. H. G. CLOSE.

**Pityriasis Lichenoides et Varioliformis.**—Dr. J. S. PEGUM.

**Necrobiosis Lipoidica (Non-diabetic).**—Dr. C. H. WHITTE and Dr. P. J. FEENY.

**Tinea Capitis (*Microsporon ferrugineum*—Ota).**—Dr. P. J. FEENY.

## Section of Neurology

President—Professor F. J. NATTRASS, M.D., F.R.C.P.

[November 4, 1954]

### Subacute Cerebellar Atrophy Following Carcinoma of the Ovaries.—A. W. DOWNIE, M.R.C.P. (for Sir RUSSELL BRAIN, P.R.C.P.).

Mrs. A. F., aged 61.

June 1953: Pan-hysterectomy for carcinoma of the ovaries, with uneventful recovery.  
15.1.54: Rose feeling well but developed vertigo over a period of one hour. This would be accompanied by vomiting unless she kept absolutely still in bed. Remained in bed ever since the onset.

18.1.54: Developed dysarthria. During the few weeks before admission she had some difficulty of vision in the right eye which subsequently cleared. At no time did she have headache or neck stiffness and there had been no loss of weight. There was no family history of similar illness.

*On examination.*—On her admission to Maida Vale Hospital in February 1954 she was vomiting constantly and was obviously suffering from severe vertigo. General examination was quite negative, in particular there was no evidence of local recurrence of her growth.

Blood pressure 150/80. Nervous system—normally orientated. No mental impairment. Severe ataxic dysarthria. Neck stiffness present for the first few days after admission. Fundi normal. Marked nystagmus on lateral gaze with alternating strabismus. Pupil reaction was normal. Slight wasting of the left thenar eminence. Power normal generally. Generalized hypotonia. Cerebellar ataxia of all four limbs. No sensory loss except for reduction of vibration sense at the ankles. Deep reflexes sluggish; plantar responses extensor.

*Investigations.*—X-rays of the skull and chest were normal. Blood picture was within normal limits. C.S.F. was under normal pressure, contained 4 lymphocytes, 120 mg. % of protein. There was a paretic-type Lange curve. W.R. was negative. Plasma proteins were normal. Pyruvate metabolism showed a gross disturbance with a fasting level of 1.4 mg. rising to 2.08 mg. in one and a half hours after glucose. Fractional test meal showed the presence of free acid. E.E.G. showed a generalized non-specific dysrhythmia.

Since her discharge from hospital, her condition has remained substantially unchanged. The vertigo of which she complained originally has subsided considerably, but is still liable to recur on sudden head movement.

*Comment.*—It was felt that this case was unusual in that the symptoms had developed seven months after the successful removal of her tumour without any evidence even now of recurrence.

Dr. Marcia Wilkinson said that she had seen a case in which a peripheral neuropathy had developed after the successful removal of a bronchial carcinoma.

### Excessive Bilateral Sinus Expansion with Mucocoele.—W. J. ATKINSON, M.D., F.R.C.S., and D. W. C. NORTHFIELD, M.S., F.R.C.S.

A.R., male, aged 56.

Admitted under the care of Mr. D. W. C. Northfield complaining of blurred vision.

Twenty years ago his friends told him that his features were changing. His head gradually increased in size so that from taking a size 6½ hat he now takes 7½. Height did not change but hands and feet altered. These changes continued for about seven years, but in recent years he has not noticed any further change apart from a steady increase in weight from 9 st. 8 lb. thirty years ago to 14 st. 6 lb. seventeen years ago. His voice became deeper during that time. He found that he could not buy gloves that were large enough for him. Says now that he has not shaved more than once every three days since the age of 20.

Seven years ago he noticed that one day he was much more thirsty than usual and was very hungry. The polyuria, polydipsia increased throughout the next day and he was admitted to hospital where he was found to have diabetes mellitus. He was treated with diet and insulin (16 units Z.P.I.) and was discharged from hospital without glycosuria. Subsequently if insulin was stopped, glycosuria returned.

He remained well until nine weeks ago when one evening on returning from work he felt sick and vomited, and then fell asleep in an armchair; three hours later he awoke and felt

MAR.

numbness of R. side of face, had drooping of R. eyelid and complained of blurred vision, which disappeared if he closed one or other eye. He also had diplopia. Later that evening he again lost consciousness and was admitted to hospital jaundiced. Jaundice lasted six weeks, gradually subsiding. During this time the urine was red and stools pale, and there was complete anorexia. Since episode of jaundice he has not been on a diet, has not had to take insulin and has had no glycosuria or lapses of consciousness, nor any excessive thirst or polyuria.

Liver function tests were as follows during the jaundiced period:

29.3.54: Serum bilirubin 6.1 mg.%; thymol turbidity 1 unit; alk. phosphatase 11 K.A. units.

5.4.54: Serum bilirubin 8.3 mg.%; thymol turbidity 1.5 units; alk. phosphatase 20 K.A. units.

9.4.54: Serum bilirubin 8.3 mg.%; thymol turbidity 1.5 units; alk. phosphatase 8.0 K.A. units.

Lumbar puncture—no cells, normal protein and globulin. X-ray chest normal.

He was discharged home free of symptoms.

His diplopia and numbness on the R. side of face steadily improved while he was in hospital, until now he only suffers from slightly blurred vision with both eyes open.



FIG. 1.



FIG. 2.



FIG. 3.



FIG. 4.



FIG. 5.

Figs. 1-5.—Mild but definite acromegalic characteristics of A.R.

For the past five years he has had occasional discharge from L. side of nose, which is thin, yellow and watery in character. For the past nine weeks this has subsided. Whilst in hospital he noticed a charcoal-like smell daily for about a few minutes, always in the L. nostril.

In 1940 he sustained a mild head injury, hitting head against a telegraph pole in blackout. Bruised L. forehead, dizzy but not unconscious. Not X-rayed.

In last three weeks lost 3 st. in weight, but thinks that he is beginning to put on weight again. His appetite is steadily improving.

*On examination.*—Fully alert and orientated. Routine intelligence and mental tests



FIG. 6.—Lateral skull view of ventriculogram showing displacement posteriorly of both anterior horns.



FIG. 7.—Lateral skull view of left common carotid arteriogram showing posterior displacement of anterior cerebral artery.

showed no abnormality. Facies typically acromegalic and coarse featured. Tongue large and broad. Fingers and toes typically spade-like. Head circumference  $22\frac{1}{2}$  in. No anosmia to peppermint, asafoetida and cinnamon, but unable to name them correctly. However, appreciates the difference between them and compared them appropriately to similar smells (Figs. 1-5).

Visual fields full to small test objects. Fundi normal. Lateral and upward movements of R. eye weak. Other E.O.M. full. R. ptosis. R. corneal reflex absent, L. present. Relative anaesthesia to cotton-wool and pin prick over R. trigeminal distribution. Other cranial nerves normal. Power, tone and co-ordination of all limbs normal. Tendon reflexes present and equal. Plantar responses flexor. No loss to ordinary sensory modalities over limbs and trunk. Gait normal apart from slight stoop. No Rombergism. B.P. 110/70. Chest—barrel shape, moves well. No other general systemic abnormality. Urine normal.



FIG. 8.—Lateral pre-operative view of skull showing eroded sella turcica, and enlarged frontal sinuses.



FIG. 9.—Lateral post-operative view of skull showing fluid level in anterior cranial fossæ (taken with patient's brow upwards).

Hæmoglobin 70%. Blood electrolytes normal. 17-ketosteroids in urine were 0.36 mg. per 100 ml. and 8.6 mg. per 24 hours. Insulin tolerance test, radio-active iodine and Kepler's test showed no abnormality.

X-rays of skull showed very considerable posterior displacement of the posterior walls of the frontal sinuses, containing air on the L. and cloudy on the R.

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Air studies and carotid arteriogram showed considerable posterior displacement of the anterior horns of the lateral ventricles and of the anterior cerebral arteries (Figs. 6-9).

A diagnosis of mucocele of the sinuses affecting the R. ocular and trigeminal nerves was made.

21.6.34: Mr. D. W. C. Northfield and Mr. W. J. Atkinson carried out a bifrontal craniotomy, removed a massive bifrontal mucocele which was arising from the region of the cribriform plate, and repaired the large defect over the cribriform plate with fascia and tantalum mesh.

Following operation a very large cavity which consisted of almost the whole of the anterior cranial fossæ continued to fill up with fluid and discharge through the L. nostril. After three weeks of daily aspirations of the cavity, the discharge finally ceased and he remained quite well subsequently.

Routine tests of pituitary function showed no alteration post-operatively. His R. ptosis, R. ocular weakness and R. trigeminal sensory loss had completely disappeared one month later.

#### Posterior Column Disease—? Cause.—ERIC C. O. JEWESBURY, D.M., M.R.C.P.

Male, aged 69. Mechanical engineer.

*History.*—July 1953: Prostatectomy for increasing tendency to urinary retention. (Cystic myo-adenomatous hyperplasia of prostate). Since operation no further bladder symptoms but has been noticeably unsteady on his feet, especially in the dark. Admits slight unsteadiness for a few years previously. No preceding illness or injury. No contact with chemicals and takes little alcohol. General health good. Able to play golf till recently.

No pains in limbs, neck or elsewhere. No stiffness or spontaneous jerks of legs. No numbness or paræsthesiæ. No difficulty in speech or swallowing. No complaint relating to vision, alimentary tract or upper limbs. Memory and concentration good. Has always been cheerful.

*Past history and family history.*—Healthy. No previous symptoms in limbs. Brother, sister, wife, two daughters and five grandchildren living and well.

*On examination.*—Alert, good colour, speech normal. Eyes: Pupils moderate size, equal, react normally. Slight nystagmus on looking to left or right. Fundi normal (myopic). Cranial nerves normal. Tongue normal. Neck movements full and painless. Slight cervico-thoracic scoliosis, with head tilted to right. Trunk, no obvious sensory changes. Heart and lungs normal. B.P. 120/105. Upper limbs: Minimal inco-ordination for finger-nose test (left more than right) and very slight diminution of vibration sense at wrists. Motor and sensory findings otherwise normal. Lower limbs: Hypotonic. No wasting, weakness or muscle tenderness. Inco-ordinate for heel-knee-shin test (left more than right). Gait: Markedly ataxic; walks on wide base; cannot toe a line. Romberg test positive. Normal shaped feet. Superficial sensibility normal. Vibration sense absent at ankles, knees and iliac crests. Postural sense markedly impaired in big toes (left more than right). Deep pain sense impaired in Achilles tendons.

Reflexes:	R.	L.	R.	L.
Arms	+	+	KJ (+)	L. (+)
Abdomen	++	++	AJ 0	0
	++	++	Pl. (↓)	(↓)

*Investigations.*—Urine: no albumin or sugar. Blood W.R. and Kahn test negative. C.S.F. clear, colourless fluid. Queckenstedt's test normal. Cells less than one W.B.C. per c.mm. Protein 35 mg.%. Globulin not increased. W.R. negative. Lange 0000000000. X-rays: Skull normal; chest—no evidence of bronchial neoplasm or recent infective changes. There is an upper thoracic scoliosis concave to the right. Cervical and upper dorsal spine: disc degenerations are present at the levels C.4, 5, 6 and 7, with considerable osteophyte formation anteriorly and postero-laterally. There is also a slight scoliosis in the lower cervical region secondary to the upper thoracic scoliosis previously noted. No intrinsic bony abnormality seen in upper thoracic vertebræ.

*Blood count.*—R.B.C. 5,100,000 per c.mm. (cells appear normal). W.B.C. 6,000 per c.mm. (neutrophils 67%). M.C.V. = 86  $\mu$ . B.S.R. = 14 mm. in one hour (Wintrobe).

*Gastric analysis.*—Initial achlorhydria but rapid appearance of free acid after histamine injected.

The differential diagnosis was discussed and it was considered that this was probably a degenerative condition of the spinal cord akin to the hereditary familial ataxias but confined to a single member of a family and delayed in onset.

[December 2, 1954]

## The Differential Diagnosis of Flaccid Paralysis

By P. H. SANDIFER, F.R.C.P.

WHAT I have to say concerns a few of the clinical situations which face the physician and in which there is doubt about the diagnosis—doubt about the site and nature of the lesion underlying flaccid paralysis. The papers which follow will tell how histological and electrodiagnostic investigations can help in resolving this doubt.

### FLACCID PARALYSIS IN EARLY CHILDHOOD

In infancy and early childhood a problem in diagnosis arises when we are confronted by the baby with flabby muscles, absent tendon-jerks, increased range of joint movement (though sometimes there is contracture) and paresis of greater or lesser degree. We may find these ingredients mixed in various proportions. The hypotonia may be so marked that the limbs dangle loosely when the child is lifted, whilst the paresis may be slight; or muscular paralysis may be profound. The symptoms may be obvious at birth, or they may appear in the post-natal period. On the one hand there may be rapid deterioration to early death: on the other hand there may be slow progress, arrest of the disease, or recovery which may be partial or even complete.

Our ideas about the meaning of this problem outlined have largely been shaped by the writings of Werdnig and of Hoffmann and by those of Oppenheim.

The main features of the syndrome described by Oppenheim as "amyotonia congenita" are of the rag-doll baby, who can be folded up into a ball because of its flabby muscles and lax joints; who has weak rather than paralysed muscles, no tendon-jerks and a tendency to improve. It now seems clear that amyotonia congenita is not a disease but is the name of a syndrome. Batten, over forty years ago, thought that some of these cases were congenital myopathies; so also did Spiller. Much more recently Aldren Turner showed convincingly that myopathy sometimes produces this syndrome. Brandt concluded from his large-scale study of amyotonia congenita (published in 1950) that most cases so labelled can be interpreted as examples of a number of diseases producing universal hypotonia—particularly "infantile progressive spinal muscular atrophy"; but he also noted a few cases which formed a heterogeneous group and did not fit conveniently into any disease-category. Adams, Denny-Brown and Pearson (1953), supporting Brandt's conclusions, suggest that some of these babies with congenital amyotonia which recover may be victims of infantile polyneuritis. They also remark the lack of satisfactory pathological studies available in such cases. It is to be hoped that this gap in our knowledge will be filled, in time, by the sort of work which Dr. Woolf and Mr. Till are doing.

It would seem that there are a host of diseases besides infantile progressive spinal muscular atrophy, myopathy and polyneuritis, which can produce the ill-defined syndrome of amyotonia congenita. These include congenital laxity of the ligaments (which some regard as an abortive form of Ehlers-Danlos syndrome); congenital universal muscular hypoplasia—and in the case described by Ford (1952) the muscle fibres in biopsy material were reported to be normal, though the muscles as a whole were small and weak; congenital myasthenia gravis; congenital atonic diplegia; mental deficiency associated with hypotonia; and various metabolic disorders such as infantile hypercalcaemia and infantile acidosis—to name but some disorders producing congenital amyotonia.

In cases of amyotonia congenita which eventually come to autopsy, the lesions much more often lie in the spinal cord than elsewhere (Greenfield and Stern, 1927; Conel, 1938, 1940; Macleod and Macdonald, 1942; Brandt, 1950). Further it seems that, in the spinal cases, it is the age of onset of anterior horn cell destruction which determines the clinical course. In contrast to the views of Werdnig and of Hoffmann, infantile progressive spinal muscular atrophy may be congenital. If the ganglion cells have been seriously damaged by the time the child is born, we see the picture of amyotonia congenita: but if they are destroyed later, the syndrome described by Werdnig and Hoffmann results—a progressive flaccid paralysis appearing typically several months after birth. These observations were made by Greenfield and Stern as long ago as 1927.

Further light was thrown on amyotonia congenita of myopathic origin when Turner (1940, 1949) showed that the syndrome can change as the years roll by. The infant with the universal hypotonia of Oppenheim's amyotonia congenita may, in adult life, present an entirely different picture. Thus in later life there may be seen the signs and symptoms, not of universal hypotonia and generalized paresis, but well-marked, though non-progressive, localized muscle wasting. Out of 4 siblings with this kind of myopathy, 3 were able to earn their living in moderately strenuous occupations. The fourth was seriously disabled, not by myopathy but by rheumatic heart disease.

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If we are to help the parents of such children with useful advice and a forecast of what will happen, we must make an exact diagnosis. Prognosis is impossible otherwise. But in making the diagnosis, we often need the help of histological and electrodiagnostic tests.

There is, I suggest, a danger in using the terms "Oppenheim's disease" and "amyotonia congenita"; for one may forget that these high-sounding names do no more than describe symptoms: they tell us nothing about where or what is wrong. It is just when we do not know what is wrong with the motor units that we welcome the assistance which the specialized skills of colleagues like Dr. A. L. Woolf, Mr. K. Till and Dr. P. Bauwens can provide.

But it is not only the *congenital* rag-doll baby which presents difficulties in diagnosis, but also those which develop symptoms later in infancy. Werdnig and Hoffmann described a syndrome of progressive flaccid, symmetrical paralysis appearing in the post-natal period, in which post-mortem revealed extensive degeneration of motor cells of the spinal cord. Subsequently it has been learned that this disease—infantile progressive spinal muscular atrophy—may be congenital or may start as late as a year or more; that it may remit for a time and even allow temporary, apparent improvement; that in its final stages it may involve cranial nerves; that it is a hereditary disease, inherited recessively (Brandt, 1950).

It has further been learned that the fatal cases, showing the Werdnig-Hoffmann syndrome may, on rather rare occasions, reveal muscular dystrophy at post-mortem; the nervous system being undamaged. It seems probable that further biopsy and autopsy studies will reveal other diseases in other situations underlying this syndrome. In problems of this kind we can often get help from histological and electro-diagnostic tests.

#### SECONDARY MYOPATHIES

In the Presidential Address to this Section on October 7, 1954, Professor Nattrass reported a series of cases of apparent muscular dystrophy, starting often in childhood, but later recovering (Nattrass, 1955). There is evidence that some of these cases are examples of polymyositis. Whether this disorder is a single disease-entity is unknown. Dalldorf and Sickles (1948) claim to have recovered the Coxsackie virus from some cases; and in a child now under my care presenting as a polymyositis, inclusion bodies are to be seen in the muscle biopsy material. Because vitamin-E deficiency has produced muscular lesions in animals, resembling those sometimes seen in man, there has been speculation about avitaminosis E being responsible for some cases of myopathy.

Nevin (1936) has described a form of myopathy of late onset; and in 1951 Rabinovitch, Gibson and McEachern have described a late myopathy which they called "Menopausal Muscular Dystrophy" and which they reported as responding favourably to vitamin E. Shy and McEachern (1951) have also described beneficial results, in cases of this kind, from treatment with cortisone and ACTH.

It is clearly of the utmost importance to determine if a particular myopathy is primary or secondary—to determine if the myopath has genetically determined muscular dystrophy, or myopathy secondary to polymyositis. Without this knowledge prognosis is impossible and we cannot predict what effect vitamin E, ACTH or cortisone may have. Here, too, is a field where the pathologist can often give the answer.

#### DISTAL MYOPATHIES

But there are other types of myopathy in which the diagnosis may be in doubt till special tests have been performed. In 1902 Gowers described a youth who developed foot-drop and, a good deal later, paresis of the finger extensors, the sternomastoids and facial muscles. But the full recognition of a distal type of myopathy and its separation from peroneal or neuritic muscular atrophy, was due to Spiller (1914). Batten (1909-10) and many others since, have described the syndrome of distal paresis and wasting which, like Gowers and Spiller, they regarded as examples of myopathy of distal distribution.

Many authors have criticized this conclusion and have suggested that these cases were atypical examples of such disorders as dystrophia myotonica or peroneal muscular atrophy.

Since Wellander published his large collection of cases in 1950, there is little doubt that a distal type of myopathy, other than that associated with myotonic dystrophy, does exist. But it is often the pathologist who provides the most important brick in the building of the diagnosis; and I have Dr. W. H. McMenemey to thank for clinching the diagnosis in 2 of my patients.

#### CHRONIC PROGRESSIVE OPHTHALMOPLÉGIA

Chronic ophthalmoplegia is a symptom which may be a component of many diseases. But the isolated symptom of chronic progressive ophthalmoplegia, which Wildbrand and Saenger described in 1921, has been shown, beyond doubt, to be produced by myopathy involving the external ocular muscles. For long it had been traditional that this ophthalmoplegia, as in Oppenheim's syndrome, often resulted from motor-cell degeneration. But Kiloh and Nevin (1951) have cast doubt on this view.

Cases of chronic progressive ophthalmoplegia described in the last century by Hutchinson (1879) and by Fuchs (1890), and much more recently by McMullen and Hine (1921), Nikitin (1929), Elliott (1939) and by Purdon Martin (1939), were probably true examples of myopathic ophthalmoplegia. I am indebted to Dr. Greenfield for reporting the histological changes of myopathic degeneration in biopsy material taken from the external rectus of a patient of mine. This single, proven case has been reported (Sandifer, 1946); but in 1951, Kiloh and Nevin reported 5 undoubted cases of chronic progressive ophthalmoplegia of myopathic origin. In 4 of these cases the diagnosis was confirmed by biopsy.

It should, perhaps, be pointed out that Blaskovitch's operation is designed to correct ptosis. Small pieces of levator palpebrae superioris are resected and inserted into the tarsal plate. Muscle biopsy can be made, at this operation, quite simply and without the patient having any reasonable grounds for complaint.

#### MYASTHENIC MYOPATHY

In their recent paper on the classification, natural history and treatment of the myopathies, Walton and Nattrass (1954) mention the term "myasthenic myopathy".

It has been widely held, for several decades, that the only significant change in the striped muscles of patients with myasthenia gravis is the presence of "lymphorrhages". It came as a surprise when Dorothy Russell (1953) reported the histological appearances in the striped muscles from 8 cases of myasthenia gravis coming to autopsy. Of these, 4 had thymic tumours (lympho-epitheliomas) and 4 had not.



FIG. 1.—Showing Type 1 lesion in heart muscle. Necrosis is occurring in a muscle fibre and there is inflammatory reaction.  $\times 230$ .

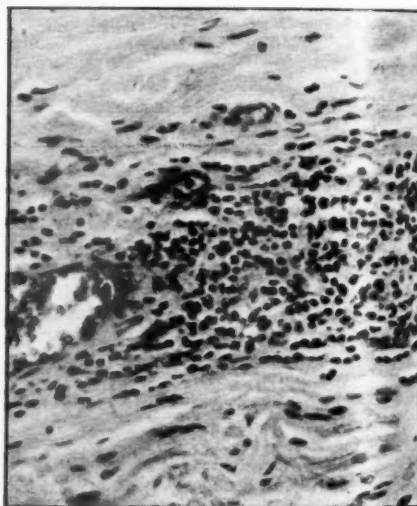


FIG. 2.—Showing lymphorrhage in section of triceps muscle.  $\times 230$ .

Three types of histological change were noted which were, in incidence, site and type of lesion, unrelated to the presence or absence of thymic tumour. The types of histological change were as follows:

- (1) An acute change is seen in which muscle fibres undergo necrosis, with resulting inflammatory cellular reaction. These muscle fibres finally disappear.
- (2) A progressive atrophy of individual muscle fibres occurs which is associated, in the later stages, with the formation of lymphorrhages.
- (3) There is a simple atrophy of different character from that of the second type. It affects single fibres or groups of fibres.

Although these histological changes are not peculiar to myasthenia gravis—for acute necrosis of striped muscle fibres may be seen in rheumatoid arthritis, Weil's disease and in other toxemias—yet it cannot be doubted that they are related to the clinical picture. As in rheumatoid arthritis, these changes are intimately related to the muscle weakness which, in myasthenia gravis, may fail to respond to Prostigmin, and to the muscle wasting which may also be a striking feature of myasthenia gravis.

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It would seem, from these observations, that there is a structural basis for the muscle wasting to be seen in some myasthenics and for the muscle weakness refractory to Prostigmin: And that the term "myasthenic myopathy" might appropriately be applied to such cases, of which the following is an example:

K. B. boy aged 13. The first symptoms occurred six months before death and took the form of diplopia and bilateral ptosis. Shortly after, his gait changed. He would walk leaning backwards with the knees bent. Within two weeks he was bedridden, dysphagic and with indistinct speech. Prostigmin produced dramatic improvement and he was discharged from hospital able to walk and free from diplopia and ptosis. He relapsed some two months later and ceased to respond to Prostigmin. He came under my care just over two weeks before he died, suddenly and unexpectedly, in an iron lung. He was, at that time, grossly emaciated, dysarthric and dysphagic with facial paresis but no ophthalmoplegia (but he was still receiving Prostigmin). There was generalized symmetrical paresis of the proximal limb muscles and trunk. The tendon-jerks were absent and he had no contractures.

Post-mortem revealed congestive heart failure, acute bronchitis and bronchopneumonia and, in addition there was widespread muscular atrophy which involved the digestive tract, heart and skeletal muscles. The affected muscles showed histological changes corresponding to Russell's Types 1, 2 and 3 lesions (Figs. 1 and 2).

The terminal neural apparatus was perfectly normal in this case; also the acetylcholinesterase end-organ.

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## The Pathology of the Lower Motor Neurone in the Light of New Muscle Biopsy Techniques

By A. L. WOOLF, M.D., and KENNETH TILL, F.R.C.S.

The following observations were originally made in Paris and Antwerp and later augmented by studies at the Hospital for Sick Children, Great Ormond Street, and the Midland Centre for Neurosurgery, Smethwick. It is a particular pleasure to record here the enthusiastic co-operation received at the Children's Hospital and the Salpêtrière in Paris, where the first muscle biopsies were carried out, and from Dr. Ludo van Bogaert at the Institut Bunge, Antwerp, where the animal studies were made.

Nowhere is more difficulty encountered than in determining the effect upon electrical function of lesions of the different intramuscular components of the lower motor neurone. This is largely because anatomical studies upon these structures are almost completely lacking in the patients upon whom the electrical studies are made. Even where biopsies are taken, current histological technique has failed to reveal the condition of the structures

in whose function we are most interested. It was in order to remedy this defect that we have followed Coërs (1952, 1953*a*, and *b*) in applying to muscle biopsies the vital staining with methylene-blue, so successfully employed by Weddell and his collaborators (Weddell and Glees, 1941; Weddell and Zander, 1950), together with the acetylcholinesterase technique of Koelle and Friedenwald (1949) improved by Couteaux (1951).

#### THE NORMAL MORPHOLOGY OF THE LOWER MOTOR NEURONE

The main trunk of the motor nerve has an approximately fixed position in any given muscle and this position can be determined by faradic stimulation, the motor nerve apparently lying underneath the "motor point". This is of considerable importance in the siting of muscle biopsies, as the motor end-plates are not distributed haphazard through the muscle but, as Coërs (1953*c*) has shown, are distributed as a band along the line joining the geometrical centres of the muscle fibres. While the motor point does not, of course, overlie all the motor end-plates, it does seem always to overlie some of them and the chances of obtaining a portion of the neural apparatus in a biopsy are greatly enhanced by taking muscle from this situation. That part of the lower motor neurone which can be studied in muscle biopsies consists of the small, intramuscular, motor nerve fibres ending in the sub-terminal nerve fibres, the terminal expansions at the ends of these fibres and the sub-neural, sub-sarcolemmal apparatus, which surrounds these expansions and forms, together with them, the motor end-plate.

The sub-terminal nerve fibres can be stained by the Bielschowsky silver impregnation technique, when they appear as a relatively simple ramification, without any marked difference in form amongst the different members of the mammalia or in different muscles from the same species.

We have been unable to impregnate the terminal expansions with silver, but have been able to demonstrate them by *in vivo* staining with methylene blue. They vary considerably in form in any one muscle, but, in our experience, are sufficiently distinctive in many species to permit identification of the species from which the muscle was taken, provided that a sufficient number of end-plates are available for examination.

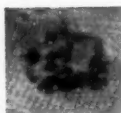


FIG. 1.

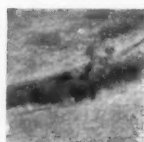


FIG. 2.

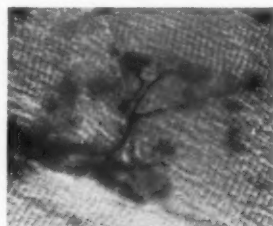


FIG. 3.



FIG. 4.

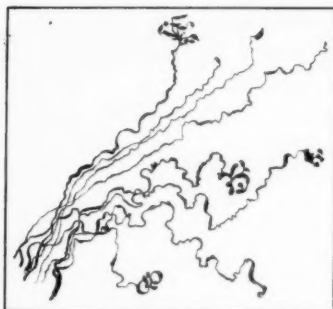


FIG. 5.

FIG. 1.—"Terminaison en plaque" from quadratus plantae of cat, stained *in vivo* with methylene-blue.  $\times 640$ .

FIG. 2.—"Terminaison en grappe" from same muscle of cat, stained *in vivo* with methylene-blue.  $\times 640$ .

FIG. 3.—Terminal arborization from the interossei of the rabbit. Stained *in vivo* with methylene-blue.  $\times 1,200$ .

FIG. 4.—"Terminaison en plaque" from brachioradialis of man. *In vivo* methylene-blue staining.  $\times 800$ .

FIG. 5.—Drawing of sub-terminal fibres and "terminaisons en grappe" in man. *In vivo* staining with methylene-blue.  $\times 163$ .

Thus, in the cat we observed a pale staining, "glomerular", "terminaison en plaque" (Fig. 1) and a darkly staining, cherry-like, "terminaison en grappe" (Fig. 2). In the rabbit, the terminal expansions more closely resembled a tree bearing fruit (Fig. 3). In the rat, Coërs (personal communication) has shown the expansions to have a plexiform arrange-

ment. None of these types of expansion could possibly be confused with those found in man which do, however, fall broadly into pale and darkly staining "terminaisons en plaque et en grappe" (Figs. 4 and 5).

The form of the terminal neural expansion finds expression in the structure of the sub-neural, sub-sarcolemmal apparatus. This apparatus is apparently composed of acetylcholinesterase and can easily be demonstrated by Koelle's histochemical technique or by vital staining with Janus green B. With either method their structure appears the same. It was studied by Couteaux in the mouse and by Coërs in man who have demonstrated the lamellated arrangement of the acetylcholinesterase and the synaptic groove into which the terminal expansion appears to fit (Figs. 6, 7). It is because of this arrangement that the form of the sub-neural apparatus is complementary to that of the terminal expansion. It seems probable that the form of the sub-neural apparatus varies, not only with the species, but also with different muscles in the same animal. The species differences are most marked between the rat or rabbit and man (Fig. 8), while the differences between the form of the sub-neural apparatus in different muscles are most marked in the small muscles of the paw and the large rectus abdominis muscle in the cat (Figs. 9 and 10). These differences may be related to the differences in the reaction of certain muscles to *d*-tubocurarine, recently demonstrated by Paton and Zaimis (1951).

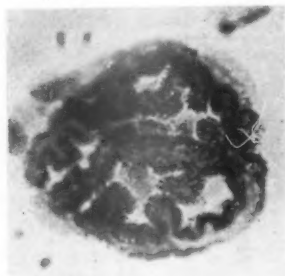


FIG. 6.—Sub-neural apparatus from a large muscle of the cat forelimb. Modified Koelle's method.  $\times 1,200$ .



FIG. 7.—Sub-neural apparatus from the gastrocnemius of a rabbit. Modified Koelle's method.  $\times 1,600$ .



FIG. 8.—Sub-neural apparatus from a human case of "myasthenic myopathy". Modified Koelle's method.  $\times 800$ .

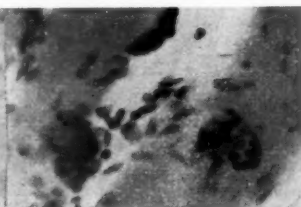


FIG. 9.—Sub-neural apparatus of the quadratus plantae of the cat. Modified Koelle's method.  $\times 330$ .

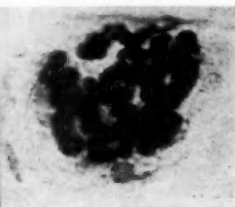


FIG. 10.—Sub-neural apparatus from the rectus abdominis of the cat. Modified Koelle's method.  $\times 640$ .

#### TECHNIQUE OF MUSCLE BIOPSY

In order to obtain as much information as possible from a biopsy, we have used the following technique, which is largely based upon that used by Coërs. If local anaesthesia is used, adrenaline should not be added to the Novocain, as this may interfere with the staining with methylene blue. General anaesthesia is more convenient in children and the motor point may be marked on the skin and the strength-duration curve made at the same time. The incision is made in the line of the muscle fibres and with two-thirds of it below the motor point, as the motor point on the exposed muscle is always distal to that on the skin. The fascia of the muscle is opened and the motor point sought directly on the skin using the same apparatus as is used for the strength-duration curve, though the current required is, of course, very small. As stimulating electrode, a trimmed piece of cotton-wool held in a wired Spencer Wells forceps and moistened with physiological saline, is quite

satisfactory. A long strip of muscle, with the motor point at its centre, is removed and placed in 10% formol saline to be stained later by the Koelle acetylcholinesterase technique. Frozen sections from this specimen can be stained with Bielschowsky combined, if desired, with the Koelle technique, and the remaining tissue used for paraffin or celloidin embedding. The motor point of the remaining muscle is again determined and with this as centre, methylene blue is injected and a piece of injected muscle is removed and treated as described by Coërs (1952). Neither Coërs nor ourselves have seen any disability result from this excision of muscle at the motor point, the reason being that only the muscle lying superficially is excised, while the main branch or branches of the motor nerve lie deeply.

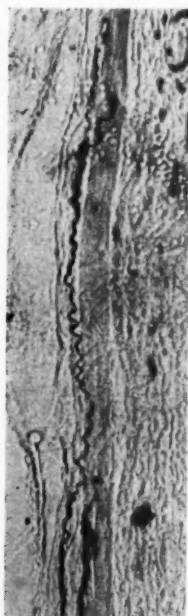


FIG. 11.



FIG. 12.



FIG. 13.



FIG. 14.



FIG. 15.

FIG. 11.—Wandering reinnervating nerve fibres from a case of Guillain-Barré syndrome. Note two poorly formed end-plates on one muscle fibre. *In vivo* methylene-blue staining.  $\times 220$ .

FIG. 12.—Drawing of bundle of fibres from same case showing beading and branching reinnervating fibres. The broadest fibres are myelin sheaths. *In vivo* methylene-blue staining.  $\times 163$ .

FIG. 13.—Drawing of terminal arborization from a case of Werdnig-Hoffmann's disease. *In vivo* methylene-blue staining.  $\times 223$ .

FIGS. 14 and 15.—Drawings of poorly formed terminal expansions in a case of Guillain-Barré syndrome. *In vivo* methylene-blue staining.  $\times 163$ .

#### CHRONIC TERMINAL MOTOR NEURONOPATHY (see TABLE I)

There is one finding which is of especial interest, and which does not seem to have been described before. We have seen it in conditions varying greatly in their natural history, though showing in common a flaccid paralysis (Table I). We have referred to the change as "chronic terminal motor neuronopathy" because there is evidence of a chronic disease of the terminal part of the motor neurone. It is, of course, true that in a muscle biopsy only the terminal part of the neurone can be visualized and that in our cases there may be changes, demonstrable at autopsy, in the proximal parts of the neurone. This was, indeed, true for Case I which showed loss of anterior horn cells (Mme. Bargeton). There is, however, some evidence that in Case VI (to be reported in detail elsewhere) the more proximal parts of even the intramuscular nerve fibres are largely free from any demonstrable structural abnormality.

It is not suggested that all the cases included in Table I were suffering from the same disease, but merely that all showed a similar change in the terminal part of the motor neurone. The changes are strikingly demonstrated by the *in vivo* methylene-blue technique,

but only crudely indicated with Bielschowsky silver impregnation and could, indeed, easily be missed with this method.

TABLE I.—CASES OF FLACCID PARALYSIS SHOWING CHRONIC TERMINAL MOTOR NEURONOPATHY

Case No.	Clinical diagnosis	Age at biopsy	Remarks
I	Oppenheim's disease	4 months	Progressive weakness of trunk and proximal limb muscles since birth
II	Amyoplasia congenita	4 months	Poor development of all muscles. Little movement of limbs. Deformed chest
III	Werdnig-Hoffmann's disease	1 year 7 months	Walked at 8 months then regression
IV	Amyotonia congenita	7 months	Floppy child. Kicks weakly. Arm held like Erb.
V	Guillain-Barré syndrome	13 years	Poor recovery from acute attack four years previously
VI	Myasthenia gravis	40 years	Good response to Prostigmin

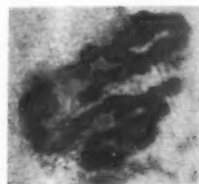


FIG. 16.



FIG. 17.

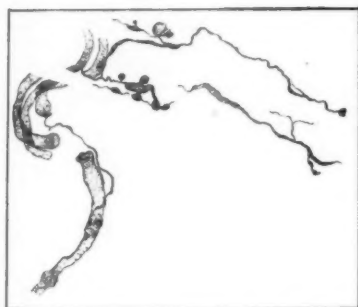


FIG. 18.



FIG. 19.



FIG. 20.

Figs. 16 and 17.—Sub-neural apparatuses from unoperated and operated sides in a rabbit whose sciatic nerve had been clamped on one side two and a half months previously. Modified Koelle's method.  $\times 640$ .

FIG. 18.—Drawing of the nerve fibres serving a muscle spindle from a case of Oppenheim's disease. *In vivo* staining with methylene blue.  $\times 163$ .

FIG. 19.—Drawing of unusually simple, possibly unduly immature sub-neural apparatuses from a floppy child aged 2½ years. Modified Koelle's method.  $\times 245$ .

FIG. 20.—Unusually large sub-neural apparatus from a case of motor neurone disease with very marked fasciculation. Modified Koelle's method.  $\times 800$ .

In cases showing "Chronic Terminal Motor Neuronopathy", the sub-terminal, neural fibres pursue a long, wandering course in isolation (Figs. 11 and 12), show beading of various degrees of coarseness, give rise to side-shoots, which are often of great delicacy and show irregular swellings, some of which appear to make contact with a muscle fibre as an inadequate end-plate (Figs. 13, 14 and 15). Many of the larger fibres terminate on the surface of muscle fibres in an unusually elaborate terminal arborization, ending in turn in bizarre, often diminutive terminal expansions. There may be as many as three end-plates on one muscle fibre, all the plates being in the same vicinity. The sub-neural apparatuses may show, in acetylcholinesterase preparations, an excessive number of very small, plate-staining units spread over a larger area than normal. To sum up, there is, in this condition, an extravagance instead of the normal economy of nervous tissue. These appearances recall Hoffman's (1953) hyperneurotized, reinnervated rat muscles, but in our cases the

attempts at reinnervation are abortive, as they are made by nerve fibres, themselves attacked by the blight, which has already destroyed the fibres they are about to replace.

What the appearances are in human muscles reinnervated by *healthy* nerve fibres, is still unknown, but in rabbit muscles, deprived of their nerve supply two to three months previously and showing evidence of reinnervation, we have observed subneural apparatuses composed of a group of small units rich in acetylcholinesterase (Fig. 16) bearing little resemblance to the plexiform apparatus seen in the corresponding muscle on the unoperated side (Fig. 17).

Returning to "chronic terminal motor neuronopathy", we have seen, in some cases, that some of the nerve fibres in the muscle spindles are irregularly swollen or beaded (Fig. 18). The spindles are not destroyed and indeed appear more numerous rather than less, this, of course, being due to the diminished bulk of the muscle. In the absence of clinical evidence of sensory loss, we have assumed that it is only the motor fibre to the spindle that is degenerate.

It is interesting to note that Case VI responded well to Prostigmin. This is not surprising in view of the tenuous connexion between many of the nerve fibres and the muscle fibre. Probably little acetylcholine can be liberated at such end-plates. It may well be that some cases of myasthenia are diseases, not of the myoneural junction, but of the sub-terminal neural arborization. We say "some" cases, because, in at least one case of myasthenia, that described by Dr. Sandifer, the terminal neural and sub-neural apparatuses were entirely normal. We have found in patients and rats, that administration of Prostigmin, before removal of a specimen of muscle, prevents the motor end-plates from appearing in acetylcholinesterase preparations, after the normal period of incubation with the substrate. With prolonged incubation, however, or, if the dose was not too great, prolonged washing in water prior to incubation, the apparatuses appeared with the normal form. Whether this would be the case in the muscle from a patient resistant to Prostigmin would be well worth investigating.

Finally, we will refer to two other interesting findings. The first of these is the report by Coërs and Pelc (1954) of immature end-plates in a floppy child that did not sit up until 1 year of age and was diagnosed as amyotonia congenita. We also have seen very simple sub-neural apparatuses (Fig. 19) in 2 similar cases, one of which had a sister with the same sort of illness. We consider, however, that it would be unwise to lay too much stress on the immature appearance of the terminal arborization and sub-neural apparatuses in amyotonia congenita, until more numerous observations have been made of the appearance of these structures in individuals of the very young age at which patients with this disease usually present.

The other observation is of very extensive sub-neural apparatuses in a case of motor neurone disease with unusually severe fasciculation (Fig. 20).

*Acknowledgments.*—Thanks are due to M. Poolvoerde for help with the animal experiments and to Mr. Peter Cull for the drawings.

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### Electrodiagnosis in Motor Unit Dysfunction

By P. BAUWENS, M.R.C.S., L.R.C.P.

ELECTRODIAGNOSIS in dysfunction of the motor unit can be likened to an attempt at tracing a fault in a telephone system by applying a series of tests at the subscriber's end. It is a restricted form of investigation but it offers the advantage of being conducted on undisturbed living structures of which the normal patterns of reaction and behaviour are moderately well established and understood. In common with other systems which transmit signals and manifest them at the receiving end, the motor unit is heir to a variety of faults which may arise from: (1) Inability to accept signals. (2) Failure to propagate them. (3) Failure to transmit them to the effector, and (4) Failure of the effector to respond to them.

To these must be added the result of: (5) Distortion of signals and (6) Spurious signals.

All the parallels exist but time will not permit of my drawing every one of them. In the motor unit, the effector consists of a large number of muscle fibres, each of which during activity gives rise to an electrical disturbance of a duration approximating to 0.5 to 1.5 msec. Provided conduction rates are the same along all the terminal axon branches and transmission delays are substantially the same at all the neuromuscular junctions, a nervous impulse arising in the anterior horn cell will cause all muscle fibres composing the motor unit to be excited almost simultaneously. Their concerted activity then causes the individual potentials to summate into an electrical diphasic or triphasic potential, not only larger in amplitude but also longer in duration (3 to 10 msec.). Delay on the part of some of the muscle fibres in contributing to the electrical by-effects of motor unit activity means a temporal dispersion which results in a less compact and more complex phenomenon with a ragged profile.

On the other hand, failure of a considerable number of muscle fibres within the motor unit to respond to an impulse gives rise to a potential of low amplitude and short duration. As this electromyographic feature characterizes primary myopathy it may—for our purpose—be termed the “myopathic pattern”. Although this “myopathic pattern” is the electrodiagnostic hallmark of classical dystrophies, it is not their monopoly. It also occurs in secondary failure of individual muscle fibre action such as is encountered in the muscle atrophy and weakness seen in thyrotoxicosis, steatorrhœa, carcinoma of the bronchus, dermatomyositis, polymyositis, periodic familial paralysis, or in impaired transmission at the neuromuscular junction—as in myasthenia gravis.

In these foregoing conditions no signs of actual denervation are detected. On stimulation of nerve trunks any decrease in muscle response is proportionate to the degree of wasting and weakness. On direct stimulation of the weak muscles with stimuli of various durations, the plotted thresholds form intensity-duration curves within normal limits, and reactions to stimuli of long duration are brisk. Nor does electromyographic exploration reveal fibrillation. Some of these secondary myopathies appear reversible as, for instance, in thyrotoxicosis, steatorrhœa and periodic familial paralysis when the determining factors no longer operate.

In another group of conditions the “myopathic pattern” is seen to co-exist with signs of denervation. This combination of the “myopathic pattern” with partial denervation can be explained on the assumption that in these cases the neuronitis causes degeneration of the terminal portion of some of the axon branches. This group, which includes those conditions classed as polyneuritis and neuromyositis, may also include those cases of dermatomyositis in which signs of mild, scattered denervation can be demonstrated.

As far as failure to propagate impulses along the main myelinated portions of the axons is concerned, it would seem that a true neuropathy is more likely to be caused by mechanical factors such as trauma, pressure from hard structures—frequently combined with traction and ischaemia—or anatomical defects, rather than by disease. Even in leprosy there appears to be some mechanical factor at play. In this type of case, it is not the muscle fibre which fails to operate within the motor unit but the motor unit within the muscle. Electromyographically, this is manifested by a simplification of the interference pattern on volition, which may be reduced to the repetitive activity of a single motor unit within pick-up range of the needle electrode. A neuropathy, whether proximal or distal—as distinct from myopathic or myelopathic affections—invariably shows signs of frank denervation unless, of course, it is a mere neurapraxia.

At first sight, there would appear to be no reason why weakness and wasting due to motor neurone involvement in the anterior horn should show any marked difference from that due to involvement in its course along a nerve trunk or root. Yet the myelopathic type of motor neurone involvement appears to have distinctive electrodiagnostic features. The most striking is the discrepancy between the muscle response on electrical stimulation of the nerve on the one hand, and volition on the other.

While tests by electrical stimulation of the nerve and muscle may show no appreciable changes, electromyographic exploration may reveal unexpected departures from the normal pattern. May I recall here that at rest the normal muscle, when explored by means of Adrian's needle electrodes, is electrically silent, while on progressively increasing volitional activity, motor unit potentials of small amplitude are at first observed, soon to be followed by potentials of larger amplitude until on full exertion the typical confused interference pattern is obtained (Fig. 1A). The amplitude then ranges between 0.5 and 2 mV. In the case of a myelopathy the silence may be broken by potentials due to spontaneous activity in the shape of fasciculation or, more rarely, minimal fibrillation.

On volition, instead of the picture just described, discrete motor unit potentials of large amplitude (2 to 6 mV) may make their appearance without any build up at the inception and only a single repetitive potential may be picked up, even on full exertion on the patient's

part (Fig. 1*b*). Frequently the tall potentials are replaced by broader, polyphasic ones, just as if temporal dispersion of activity were occurring in the muscular component of an outsize motor unit (Fig. 1*c*). This temporal dispersion, when extreme, may cause the tracing to assume the appearance of a "myopathic pattern", and I feel that I may at times have fallen into this trap. The distinguishing sign is that in myelopathies the small potentials occur in compact trains rather than as continuous patterns. Needless to say, when the disease has progressed to the point where actual motor neurone destruction becomes extensive, the signs of frank denervation become evident in the muscles affected, but this is a later development in most cases.

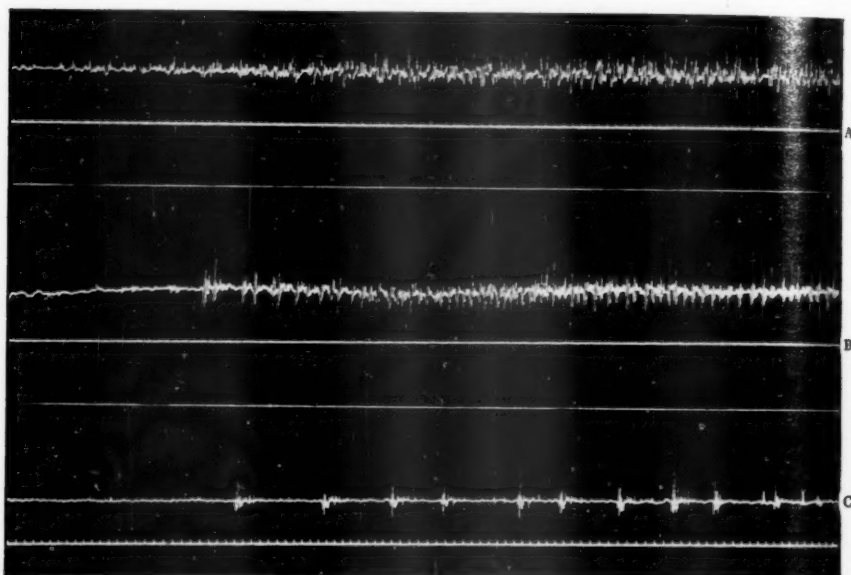


FIG. 1.—Electromyographic patterns at the inception and on progressively increasing volitional activity. *A*, in the normal, showing initial small potentials followed by larger ones building up to a normal interference pattern. *B*, in affections of the cord showing abrupt appearance of large discrete potentials with increasing frequency. *C*, as in *B* but showing broken-up patterns possibly due to temporal dispersion of muscle fibre activity (Time scale — 10 msec.).

It is not easy to explain these eccentricities in the behaviour of motor neurones in the early phases of myelopathies. The fact that nerve excitability and conduction remain almost unimpaired but coupled with a form of apraxia on volition, at first suggests impaired synaptic transmission in the anterior horns. Unfortunately for such a postulate, exaggerated reflexes frequently co-exist. Again, to explain the distal phenomena of fasciculation and of temporal dispersion, one is driven to assume that some changes in or around the anterior horn cell can cause modification in the properties of the neurone's membrane distally—particularly at the neuromuscular junction.

Several hypotheses have been put forward to account for the large amplitude potentials, of which one is synchronization of motor-unit activity through neurone interaction. Another presumes the existence of large motor units of which the activity is normally masked by the earlier recruitment of small motor units, but which is revealed when the small motor units fail to come into play through their preceding apraxia or destruction. There is yet another possible explanation which has to take into consideration the servo-mechanism which plays such an important part in the remote control of muscle.

It is now generally accepted that the link between a muscle and the appropriate segment of the cord consists of a minimum of one afferent and two efferent neurones. The efferent neurone which supplies the intrafusal fibre primes the muscle. The afferent neurone from the spindle signals back information concerning the resulting situation in the muscle and initiates in the anterior horn the recruitment of the motor units proper, which finally cause the shortening of the muscle and the release of tension in the spindles.

The term "cybernetics" has been coined to cover the study and development of these

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systems in which precision is obtained by comparing the result of an initial action with the predetermined objective—any difference between the two being utilized to direct further action towards the objective. While accurate, such complex systems are more vulnerable and more sluggish than the simple ones based on direct control. In the case of muscles, physiologists tell us that for urgent action, as in an emergency, immediate excitation of the motor units—cutting out the servo-loop—is obtainable, probably at the expense of precision and restraint.

In a locomotor mechanism embodying this principle, should the priming of the muscle come to fail, muscle movement would still be possible by resorting to the direct paths and possibly result in the electromyographic pattern peculiar to myelopathies. Failure of the priming mechanism alone should not, of course, impair the stretch or tendon reflexes, while failure of the afferent portion of the servo-loop should give rise to the same electromyographic pattern, but depress those reflexes.

In an article entitled "Étude Électromyographique des Troubles de la Sensibilité Profonde", Lesny, Dreschler and Obrda (1950) describe the effects in man of deafferentation by section of one or two posterior spinal roots on the electromyographic pattern. They observed on volition: (1) A diminution of the potentials. (2) Almost complete disappearance of low amplitude motor unit activity, and (3) The presence of some duplication.

These are departures from the normal which characterize myelopathies and, without wishing to overstress the similarity, I draw attention to these observations merely to show how an apparent dysfunction of the motor unit could result from extraneous causes and produce some of the electromyographic features noted in the early phases of myelopathies (Fig. 2).

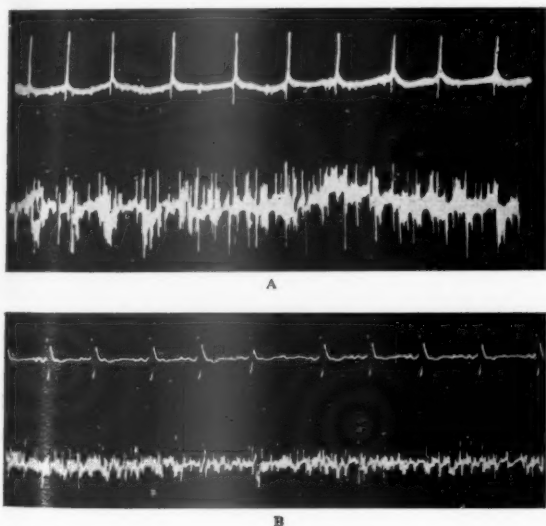


FIG. 2.—Illustrating the similarity of electromyographic patterns on volition in deafferentation and in motor neurone disease. A, obtained by Lesny *et al.* (1950); reproduced by kind permission of Dr. I. Lesny and of Messrs. Masson et Cie. B, obtained by the author. Each abnormal tracing is matched by a normal interference pattern obtained with the same equipment.

It is a melancholy thought that electrodiagnostic methods which may help to differentiate between myopathic and myelopathic disorders, and between distal and proximal neuropathies, will not readily—by themselves—distinguish between a motor neurone disease and cervical spine abnormalities capable of simulating this condition. However, when it is realized that a disc herniation of the anteromedial type is virtually a mechanical form of myelopathy, the mortification becomes more bearable.

In this connexion, Dr. Kendall will outline the clinical features of a case which I investigated for him and which illustrates this particular point. In this man the wasted muscles of the shoulder girdles and the biceps on both sides all displayed the electrodiagnostic feature generally associated with a disorder of myelopathic origin.

I feel that the correlation of the clinical picture and a study of the morbid pathology by modern methods as described by Dr. Woolf will finally give us the explanation of this problem, though possibly at variance with the orthodox concepts.

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**Dr. David Kendall:** The patient in whom Dr. Bauwens and I have been interested presents clinically a difficult diagnostic problem. The man, aged 58, first attended hospital two years ago for investigation of a single epileptic attack; no cause was subsequently found for this. He stated that at the age of about 14 he had started to complain of weakness followed by wasting of the muscles of the shoulder girdle and of the upper arms and that this had progressed slowly for the following four or five years. In 1915, at the age of 19, he attended St. Thomas's Hospital where he was told that he was suffering from a muscular dystrophy. From that time until he attended hospital two years ago he is reasonably sure that no further adverse progress had taken place. There is no history of similar affliction in his family and his own early history was uneventful. He was, however, knocked down by a bicycle at the age of 2 but has no knowledge of the injuries which he sustained.



FIG. 1.—Showing persistent deformity of the cervical spine in flexion and extension, and wedge deformity of the fifth and sixth cervical bodies.

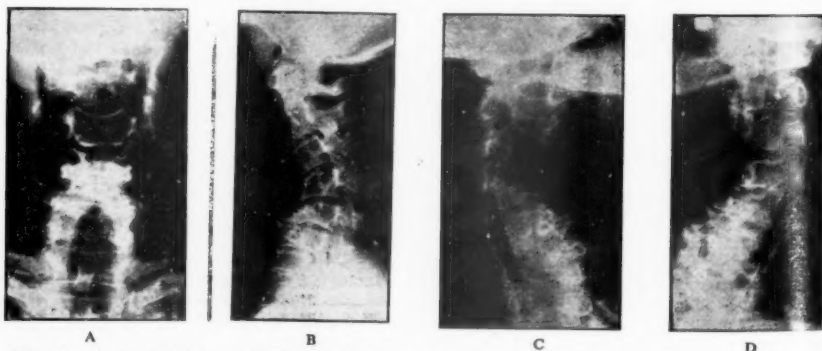


FIG. 2.—Anteroposterior, lateral and oblique views of the cervical spine to show misalignment, loss of the lower disc spaces and encroachment on the intervertebral foramina.

Examination two years ago showed him to have widespread symmetrical wasting of the muscles of the shoulder girdle, the biceps and to a lesser extent the triceps muscles. The lower part of the trapezius and the posterior cervical muscles were also wasted. Occasional

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fasciculation was seen in the right biceps. The tendon reflexes in the arms were normal, those in the legs were exaggerated with clonus. The abdominal reflexes were present and the plantar responses flexor. Sensation was quite normal. Neck movements antero-posteriorly were limited but painless. There was a cervical lordosis (Figs. 1 and 2). It was considered then that this man might be suffering from the delayed effects of a cervical cord injury or from a very unusual type of motor neurone disease, but as the condition was of long standing and apparently non-progressive no further investigation was contemplated.

In the course of the past two years his condition has deteriorated. The wasting of the shoulder-girdle muscles has become more severe and the extensor muscles of the wrists and fingers are becoming weak; he is also developing a spastic weakness of both legs. There is now widespread fasciculation in the affected muscles, the tendon reflexes are universally increased with inversion of the radial reflexes. No sensory disturbance has appeared, nor has there been any pain in the neck. The interest of this case lies in the fact that electromyography has confirmed what is now clinically obvious, that this man has a condition arising from damage to the cervical region of the spinal cord, although superficially his condition, which has been present for many years, resembles a myopathy. The latter diagnosis would presumably have been found more likely prior to the appearance of physical signs in the lower limbs. It would be easy to infer some progressive interference with the blood supply to the cervical cord, in view of the resemblance of the distribution of the wasting to that following occlusion of the anterior spinal artery, but it would be equally difficult to prove such a hypothesis.

**Professor Ruth E. M. Bowden:** The patterns of innervations which were seen in the beautiful preparations made by Dr. Woolf resemble those found in delayed reinnervation after peripheral nerve injuries in man. It would be interesting to know the appearance of the muscle fibres themselves, for in a case of muscular dystrophy of late onset the same pattern of innervation was observed. In this case the electromyogram gave evidence of potentials which were indistinguishable from those of fibrillation. It has been suggested that in this case the muscles became denervated as a result of disease of the muscle fibres themselves and the pattern of delayed reinnervation was due to the attempts of nerve fibres to reform connexions with grossly diseased muscle fibres which were still capable of contracting and therefore gave the fibrillation-like action potentials. In prolonged denervation there is no evidence of fatty change within the muscle fibres, although fat is laid down around them, and this would seem to be a useful method of distinguishing between paralyzes of myogenic and neurogenic origin.

**Dr. John N. Walton:** Dr. Sandifer has certainly given us a very comprehensive catalogue of the causes of flaccid paralysis, particularly those occurring in infancy, and giving rise to the clinical syndrome of "amyotonia congenita". I would like to add yet another condition to the list, namely von Gierke's glycogen storage disease. Infants suffering from this condition may show a syndrome of generalized flaccid weakness and hypotonia, and may be difficult to distinguish from the Werdnig-Hoffmann disease, save by the presence of cardiac enlargement, splenomegaly and hepatomegaly. Cases of this type have been reported by Ford (1952) and others. Another condition which I have found to produce serious diagnostic difficulty is one which I can only refer to as "the syndrome of the limp child". There seem to be certain children who are remarkably limp and hypotonic at birth, and who sit up and walk very late, but yet are mentally alert and eventually develop normally. It would be of the greatest interest to carry out muscle biopsy on such children using the technique described by Dr. Woolf, to see whether they have the type of end-plates which he referred to as immature. In my limited experience, standard staining methods reveal no abnormality in the muscle of such patients; biopsy is often necessary to distinguish the condition from the more serious diseases which Dr. Sandifer has discussed. To use Dr. Woolf's technique would probably be justified in cases of diagnostic difficulty, and might well give us very valuable information.

Dr. Sandifer asked whether polymyositis is a single entity. I think that there is increasing evidence to indicate that the typical clinical picture, often looking so very like that of muscular dystrophy, when combined with the characteristic muscular pathology, gives us a distinctive syndrome. Probably most such cases, even when skin changes are absent, are related to the other conditions in the "collagen-vascular" group. Dr. Sandifer also referred to the finding of inclusion bodies in the muscle biopsy from one such case. I think that this finding should be interpreted with caution, and is not necessarily indicative of an infective cause. The histological appearances of muscular regeneration are generally found in muscle from cases of polymyositis; the multiple nucleoli of proliferating sarcolemmal nuclei in regenerating muscle may look very like inclusion bodies, particularly when they are rather irregular, the so-called rhombosomes of Millar (1934).

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**Mr. Kenneth Till**, in reply to a question, said that it should not be difficult to obtain the help of a surgeon since the technique involved was very simple and the operation took only about half an hour.

He emphasized the fact that there was no evidence of further loss of power in a muscle from which a biopsy specimen had been obtained.

**Dr. A. T. Richardson:** Dr. Bauwens in his paper has drawn attention to a condition which he calls distal neuronitis, the electrodiagnostic criteria of which appear to be abnormal intensity-duration curves and fibrillation potentials with a full interference pattern of short duration and polyphasic motor unit potentials on volition. It is, of course, possible to obtain these findings in a recovering lower motor neurone lesion but apart from this do they indicate a primary lesion of both the lower motor neurones and muscle fibres, a primary muscle fibre lesion with the extraordinary occurrence of abnormal intensity-duration curves and fibrillation potentials or, as Dr. Bauwens suggests, a lesion of the distal part of the lower motor neurone with a secondary failure of muscle fibre function?

I should also like to refer to another group of electrodiagnostic findings for which there is no satisfactory explanation. This consists of normal intensity-duration curves with electrical silence at rest and a reduced interference pattern of normal duration motor unit potentials on volition. Is this indicative of a myopathy with residual normal motor unit potentials or of some form of neuropathy in which the signs of lower motor neurone degeneration cannot be obtained?

**Dr. Geoffrey H. Bourne:** I would be very interested to know how many normal muscle biopsies stained by this methylene-blue technique Dr. Woolf has taken. One wonders how many of the kinks and beading demonstrated in his dystrophic muscle biopsies are, in fact, abnormalities. I should like also to say that it is difficult to understand why the assumption is made that in any dystrophy the lesion is always neurological. There are profound changes in the structure and histochemistry of dystrophic muscle and perhaps in some cases the lesion may be in the muscle itself.

The President referred to the histological differentiation of muscular dystrophy and polymyositis. Increasing experience showed that this might be difficult, the changes seeming to depend chiefly on the acuteness of the condition: if the onset was rapid, the appearances of myositis were distinctive. But there are cases which progress very slowly or become arrested, and in these the histological distinction from dystrophy is far less clear. Enlargement of fibres, variation in size and fat infiltration can occur in both. On the other hand any evidences of inflammatory reaction, and especially of regeneration of muscle fibres, are inconsistent with muscular dystrophy.

He had under observation at present 3 women, 2 young, with a clinical picture suggestive of polymyositis, but the histological appearances at first were regarded as indecisive for the reasons stated. On the other hand, he had also under observation a man aged 50 with a picture almost identical with facioscapulohumeral dystrophy except that the onset was only two years ago, there was no family history of any similar condition, and deterioration had been rapid, especially in recent months. Here the biopsy picture was that of florid myositis and the initial reaction to cortisone was impressive.

Unfortunately the electromyogram may not help as it gives a picture of primary muscle disease but does not clearly differentiate the types of this.

**Dr. Woolf**, in reply to Professor Bowden, stated that all of his 6 cases of chronic terminal motor neuronopathy showed groups of atrophied or poorly developed muscle fibres indicative of denervation or defective innervation. The case (No. 6) of myasthenia gravis, however, also showed the basophilic staining and vacuolation of isolated fibres reported by Russell (1953) in her fatal cases of myasthenia gravis as Type 2 change. This appearance is regarded by some pathologists as characteristic of a primary myopathy. In this case, like that of Professor Bowden's it is difficult to know whether the primary change is in the muscle fibre or the terminal neural apparatus. What is needed is further studies with vital staining of the nerve-endings in cases of indisputable primary myopathy.

In reply to Dr. Bourne, Dr. Woolf stated that his own experience of vital staining of nerve-endings in normal muscles was small, but he had had the opportunity to examine Dr. Coërs' much larger collection and had been able to form a good idea of the range of normal appearances. Many of these had been illustrated in Dr. Coërs' publications (1952, 1953) and included none of the features which had been demonstrated to the meeting.

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# United Services Section

President—Sir LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P.

[December 2, 1954]

## DISCUSSION ON SOME ASPECTS OF ANKYLOSING SPONDYLITIS

Lieut.-Colonel J. P. Baird:

### Symptoms and Diagnosis

Ankylosing spondylitis is a disease of young adults, otherwise fit young men being mainly affected. Since the great majority of cases arise between the ages of 15 and 35 it is very much an illness of the Service age group. Buckley (1945) has stated that the striking feature of rheumatic disease in the 1939-45 war had been the number of cases of spondylitis in all the Forces.

It is a condition in which diagnosis may be extremely difficult or indeed impossible in the early stages and in which incorrect diagnosis is only too frequent. Two months ago a question was asked in the *British Medical Journal* (1954) beginning "There appears to be a great deal of confusion with regard to the early diagnosis of ankylosing spondylitis and I should be grateful if you would kindly let me know the early diagnostic features . . ." In the midst of this confusion the doctor may easily lose the confidence of his patient by failing to recognize the significance of certain symptoms.

The end-results of spinal and hip ankylosis in bad position are pathetic, these people being called "spondylitic wrecks" by Gilbert Scott (1942). The only hope of minimizing such results is early diagnosis and efficient treatment before fixed deformity in bad posture can appear. It is well recognized that the disease in some patients will "burn out" in good position and become painless with little disability, whereas in others it will advance to a severe degree before the diagnosis is made.

We should therefore first examine our record of diagnostic effort. In the past three years 68 cases, all males, have been seen in the Queen Alexandra Military Hospital. Fig. 1

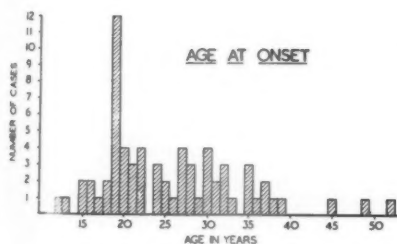


FIG. 1.

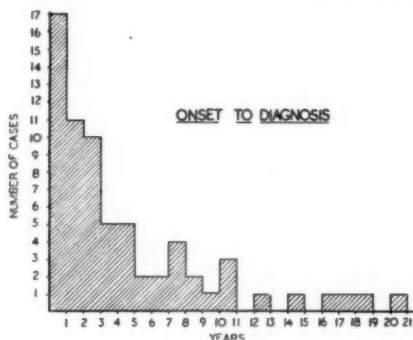


FIG. 2.

shows the ages of the patients at the onset of the disease. The duration from onset of symptoms to diagnosis is shown in Fig. 2. A comparison of our figures with a large series reported from Newcastle in 1949 (Mowbray *et al.*, 1949) is given in Table I.

TABLE I.—YEARS TO DIAGNOSIS

Years	Mowbray <i>et al.</i> (1949)	Present series (1954)
0-1	9	17
1-2	32	11
2-5	57	20
5-10	21	11
10+	18	9
Totals	137	68

It must not be thought that these long intervals represent failure in diagnosis. Many patients have such minor symptoms that they do not report sick for a long time. An extreme example of this is the following case.

**Case 28.**—An officer aged 33 with fourteen years' service was found at a routine Pulheims examination to have a stiff back and ankylosing spondylitis was diagnosed. On direct questioning he admitted to gradual progressive stiffness of the back for four years but denied any pain and had never reported sick. His spinal flexion was only 20 degrees and X-rays showed a typical "bamboo spine".

This is one of two patients in our series who were discovered on routine examination, while serving. Several others were found when being examined for an unrelated complaint. A number of patients, however, do have major symptoms and report sick, but the diagnosis is missed.

**Case 18.**—A Warrant Officer aged 41 had recurrent pains during twenty-one of his twenty-three years' service and had reported sick many times. His pain in the back and down the legs was diagnosed as "sciatica"; his pain between the shoulders and in the back as "neuritis" and his stiffening neck as "torticollis". The correct diagnosis was finally made five months before the termination of his long and honourable service.

On the other hand we have a patient who was diagnosed in a fortnight from the onset of symptoms.

The textbook picture of the advanced case is misleading and unless one is aware of this it is difficult to realize how slight, brief and diverse the early symptoms may be.

#### SYMPTOMATOLOGY

By far the commonest presenting symptom is pain or pains. Stiffness is variable, less troublesome to the patient, and often of later onset. Only 3 patients could not be induced to admit to any pain at all. The character of the pains can also be most variable. Short acute attacks of stabbing or sharp pain may occur at intervals, with periods of complete freedom in between, lasting many months. Or, commonly, the pain is persistent, nagging, and aching with acute exacerbations. Attacks may be so slight that the patient does not report sick but finds relief from a few aspirins, or "works the pain off" by exercise. Pain may be increased by coughing or sneezing.

The site of pain is just as variable and almost any part of the body can be affected, causing such diverse complaints as occipital headache or painful heels or toes.

39 patients (57.3%) complained first of pain in the region of the lumbar spine and pelvic girdle—low back pain, pains in the hips and buttocks or down the thighs being most common.

In 18 (26.5%), pains had arisen in the shoulder girdle, neck, chest, or thoraco-lumbar regions. In the remaining 8 (11.7%), painful peripheral joints were first noticed—knees, ankles or feet, elbows, wrists, or hands. But in addition, at some stage or another, 19 patients (28%), have had some peripheral joint symptoms.

The "pre-spondylitic wandering pains", so aptly named by Scott (1942), are indeed confusing and may suggest any diagnosis other than the correct one. But Dudley Hart and his colleagues (Hart *et al.*, 1949) have drawn attention to certain features of the pain and stiffness which should arouse suspicion. A complaint that the condition is worse first thing in the morning or after a rest was made by nearly half our patients (30–44.1%). As the day goes on or when exercise loosens up the movements there is relief. Pain on sitting is distressing, leading to the use of air rings or cushions to relieve pressure on tender buttocks or ischial tuberosities. Severe discomfort and pain in bed at night affected 21 of 68 patients (30.9%). One officer found his bed so uncomfortable at one stage of his illness that he took to sleeping in a chair at night. Fortunately his buttocks and ischial tuberosities were painless. Some patients complain that exercise makes the symptoms worse.

The combination of pain and stiffness often makes dressing difficult, boots and garters being particularly troublesome. Difficulty in fastening the Army gaiter is a frequent spontaneous complaint. Whether one sits down or stands up with one foot on a chair to fasten the gaiter, the attitude required is one of marked flexion with rotation of the lumbar spine, considerable flexion and internal rotation of the hip-joint and flexion of the knee. These movements of lumbar spine and hip-joint cause much pain and discomfort in the early stage and may be quite impossible for the advanced spondylitic.

Stiffness of the spine and thorax may progress rapidly over a short period or so imperceptibly through the years as to be hardly recognized by the patient at all.

Loss of weight has been a marked feature occurring in 20 (29.4%) of our patients. It is or a history of this complaint is strong supportive evidence of the disease. Non-specific urethritis may be misleading but may sometimes lead to the correct diagnosis.

In acute cases a feeling of ill-health is common, or a febrile illness may occur, but in the average case no change in the general health has been noticed.

## DIAGNOSIS

It seemed that it might be profitable to examine certain groups more closely:

- (1) The cases of short duration from onset to diagnosis.
- (2) The cases of long duration to diagnosis.
- (3) The cases with onset at a young age.
- (4) The cases in which other diagnoses had been made.

(1) *Cases of Short Duration to Diagnosis*

Diagnosis was correctly made in 17 instances under one year from the onset of symptoms. The record is held by those who diagnosed a case in a fortnight.

10 of these 17 complained of lumbo-sacral or spinal symptoms and the diagnosis was quickly made. They were mostly referred to orthopaedic surgeons for low back pain, and those officers quickly recognized the cause.

Of the remainder, one presented with non-specific urethritis and peripheral joint symptoms and another with two attacks of non-specific urethritis and pain in the back. Both were at first thought to be cases of Reiter's syndrome and because of this interesting possibility were subjected to careful investigation in hospital and the spondylitis discovered. The third patient had a much more severe illness with fever, and marked peripheral joint pain and swelling following an attack of bacillary dysentery. For some time he was regarded as a case of post-dysenteric arthritis.

The fourth had been ill with a long-continued fever, with pain and swelling of many peripheral joints, backache and chest pains, complicated by malaria two weeks before the onset, and by finding malarial parasites again in the course of the illness. A combination of malaria and brucellosis had seemed the most likely explanation of this illness.

The fifth, a young officer, was admitted to hospital in Korea with dysentery, and his stiff back was noticed. On further enquiry he admitted to mild back pain and stiffness which had only been a nuisance and had not prevented him carrying out his duties in a forward area.

The sixth patient complained bitterly at first of stabbing pains in one buttock and was diagnosed at three months. The seventh patient presented with a painful stiff neck and chest.

In 7 patients a curious symptomatology was only with some difficulty recognized as spondylitis. It emerges from the records of all 17 that these early cases were diagnosed or suspected by doctors who clearly had the condition in mind and were aware of its diverse symptoms, while carrying out a careful detailed physical examination and investigations.

(2) *Long Duration Cases*

The time taken to diagnosis seems abnormally long in ten instances—ten years or over—and these were grouped to see if any common factor emerged.

3 patients dated their symptoms back many years to a severe injury with fractured spine and a long spell of hospital treatment. A fourth had a history of severe injury with fracture of a vertebral body. X-ray evidence of an old fracture was found in all 4.

2 patients had severe gunshot wounds about the time of onset of symptoms; severe wounds of the left arm in one instance, and of the right thigh and right knee in another. One patient injured his neck from diving into shallow water.

In 6 of 10 cases, therefore, a history of severe trauma was obtained at or about the time of onset, in 4 the trauma being to the spine.

The possibilities obvious are:

(i) In retrospect we may have attributed to the ankylosing spondylitis symptoms which were in fact due to the injuries.

(ii) The symptoms during these long periods may have been regarded by the patients and only too easily by their doctors as due to the injuries. This would be supported in 4 patients by X-ray changes of an old spinal fracture.

(iii) The third and most interesting possibility is that trauma played some part in determining the onset of the disease.

A relatively minor injury such as a fall from a tank or from a truck, though not severe enough to require hospital admission, often seems to focus the attention of the victim on his back. He may attribute his symptoms to this injury, but a careful history will often reveal that symptoms have in fact been present for some time before the incident. It has on several occasions occurred to me that some restriction of movement makes these men clumsy and the fall is the result of the disease. I do not, however, wish to make too much of this point since the falls I have mentioned are among the commonest injuries to soldiers.

Of the 4 remaining patients in this group, one gave a history of recurrent iritis sixteen years before the onset of other symptoms; 2 had misleading peripheral joint involvement for years before classical symptoms and only one had reported sick repeatedly with complaints which might have been recognized earlier.

(3) *Onset Under 19 Years of Age*

9 patients were found to have symptoms starting before the age of 19. Peripheral joints were first involved in 4 of this group, with pain, stiffness, swelling, or effusion, for long periods before lumbar or pelvic symptoms appeared; one of them complained of pain and swelling of the finger, shoulder, knee and ankle joints and noticed that the pain disappeared as the joints became swollen. Onset in the remaining 5 patients was in the more usual lumbar, hip, thigh areas with a history of iritis in two instances.

(4) *Errors in Diagnosis*

In our series 31 patients had been given another diagnosis at some stage in the past; and a number had been called several different conditions (Table II).

TABLE II.—OTHER DIAGNOSES

Prolapsed intervertebral disc	11	Sacro-iliac strain	..	..	..	1
Sciatica	3	Torticollis	..	..	..	1
Rheumatism, fibrositis, neuritis	..	4	Pleurisy	..	..	1
Old fracture spine	..	4	Post-dysenteric arthritis	..	..	1
Reiter's syndrome	..	..	2	Undulant fever	..	1
Gout	..	..	2	Psychoneurosis	..	1
Gonococcal arthritis	..	..	1	Diagnosis not known	..	6
Arthritis of hips	..	..	1			

This table is not shown in any critical sense, but to pick out the diagnoses of which we must beware, and which we must test carefully in young subjects. It shows that prolapsed disc or sciatica is the commonest error. It is unfortunate that complete rest or a spinal plaster will often relieve the pain temporarily, thus seeming to confirm the diagnosis, but allows of rapid and often irremediable stiffening of the spine and chest. Sciatic-like pain not extending below the knee, particularly with equivocal signs of a prolapsed disc should always arouse suspicion of ankylosing spondylitis in a young patient. The diagnosis of prolapsed disc should be reviewed if pain recurs rapidly after an initial successful period of treatment or if increasing stiffness becomes apparent.

Our aim is earlier diagnosis, therefore all medical officers must be aware of the significance of symptoms of a minor nature and should be on the look-out for cases. Once the condition is suspected a great deal can be done. It is important to remember the dictum of Gilbert Scott (1942) that all patients with indefinite rheumatic pains appearing soon after puberty should have X-rays of the sacro-iliac joints. If our suspicions are aroused we should look for the four cardinal diagnostic features stressed by Dudley Hart and his colleagues (1949): spinal stiffness, diminished thoracic expansion, raised E.S.R., and radiological changes in the sacro-iliac joints. In this way we may further improve our diagnostic effort.

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## Lieut.-Colonel R. J. G. Morrison:

*Complications*

My main subject is the complications that have occurred in the group of patients whose symptoms have been discussed by Colonel Baird.

This group consists of 68 patients seen by us as in-patients in the last three years.

Perhaps the term "complications" is not really the most suitable to use in connexion with ankylosing spondylitis, for we are not dealing with an acute illness followed by a definite complication, but with a slowly progressive complaint whose onward march is punctuated by a series of episodes—milestones, in fact, on the stony road of spondylitis.

Before proceeding with the complications in particular I should like to make a few general observations.

Firstly, although some of the complications are readily explainable others are not so, and it is, for example, difficult to see why spondylitis should be complicated by iritis or by urethritis.

Complications may occur at any stage of spondylitis. They may be present before the disease apparently manifests itself, or may intrude during a quiescent period, and even declare themselves immediately after a course of deep X-ray treatment. Some of our patients have had more than one complication and we have noticed a tendency for different

complications to occur together. Naturally enough, it is in the long-standing cases, where a larger segment of the life history of spondylitis is covered, that complications have been commonest. We have encountered complications in 31 of our 68 patients, an incidence of 46%.

### Iritis

Iritis is a well-recognized complication. Gilbert Scott (1942) found it in 20 of 300 cases, and both Buckley (1945) and Sorsby (1951) give its incidence as 10%. Sharp and Easson (1954) found iritis in 19 cases out of 242 patients with spondylitis.

Its presence has been used by some as an argument in favour of the tuberculous nature of spondylitis, and, paradoxically, by others as evidence of a gonococcal causation. It is not often encountered as an acute condition. More frequently only the past history of iritis is obtained, but ophthalmological examination will reveal the tell-tale signs of past infection. However, we have seen it in acute form in hospital in 3 cases.

Multiple attacks of iritis are common. Of our 8 cases in only 3 instances were the attacks single. 1 patient had as many as 13 separate attacks spread over a period of ten years.

The infection may attack first one eye and then the other but we have not seen both eyes affected simultaneously. We have seen it occur at the end of a course of deep X-ray treatment.

The time-relation between the onset of spondylitic symptoms and iritis is interesting. In 3 cases iritis preceded the onset of spondylitis, in one patient by as long a period as seventeen years.

Fig. 1 shows this relation, and the spacing over the years of the attacks of iritis.

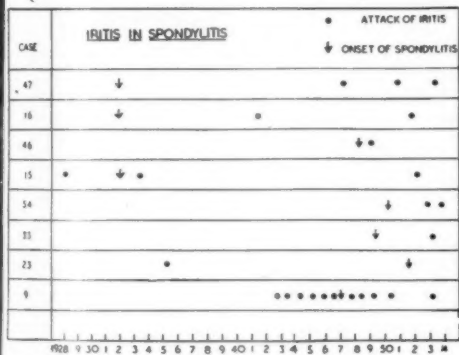


FIG. 1.

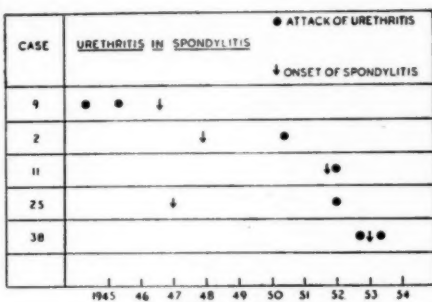


FIG. 2.

### Urethritis

5 patients have had urethritis. In 2 cases this took place just before the onset of other symptoms. In 2 patients a second attack occurred.

Usually the urethritis has been quite benign but in one patient it was followed by an attack of epididymo-orchitis. In another a urethral stricture developed which eventually necessitated a suprapubic cystotomy and even now this patient still has periodic urethral dilatations. In fact, it was only after the patient was confined to bed for his operation that the spinal symptoms became manifest. This onset of symptoms after a period of bed rest is quite common in spondylitis.

The association between gonorrhoea and spondylitis has been much stressed in the past, and the gonococcal poker-back was familiar to doctors of thirty years ago.

However, I am not convinced of there being any relation at the present time between gonorrhoea and spondylitis. Only one of our patients gave a past history of gonorrhoea and this occurred after the onset of spondylitis. On the two occasions that we have had an opportunity of examining the urethral discharge a vigorous search for gonococci has been negative. It is tempting to assume that many of the so-called gonococcal cases of years ago may well have been ones of simple urethritis.

Fig. 2 shows the relationship between the urethritis and the onset of spinal symptoms.

### Peripheral Joints

Before discussing the involvement of peripheral joints I should like to make it clear that I have only included cases which have demonstrated considerable joint involvement, and which have shown redness, swelling or both.

The involvement of peripheral joints is well recognized and occurred in 18 out of 60 cases reported by Boland and Present (1945).

In only 8 of their cases were the joints affected before the onset of spondylitic symptoms. Our experience has been different and we have found that of our 9 cases 8 occurred before the onset of spinal symptoms. This experience has been confirmed by that of the R.A.F. at Chessington, where Milligan and Wynn Parry (1954) have found that in 25% of their cases a peripheral arthritis has been the first manifestation, the knee- and ankle-joints being the most frequently involved.

This at once raises serious problems with regard to diagnosis for it is wellnigh impossible to make a correct diagnosis at the stage when arthritis is the only abnormality. This fact stresses the importance of having the sacro-iliac joints X-rayed in any atypical arthritis in a young subject, and perhaps the same may be said with regard to iritis.

Table I well illustrates this. I have tabulated the date of involvement of the peripheral

TABLE I.—INVOLVEMENT OF PERIPHERAL JOINTS PRIOR TO SPONDYLITIS

Case	Joints involved	Date	Diagnosis	Spine
9	Ankle (L.)	1937	Reiter's syndrome	1947
39	Knee (L.)	1952	Post-dysenteric arthritis	1952
40	Knee (L.)	1947	"Arthritis"	1947
11	Elbow (R.)	1952	Reiter's syndrome	1952
33	Ankle (R.)	1948	(Plaster)	1948
56	Knees, Ankles (R. & L.)	1942	Gout	1949
31	Knee (R.)	1951	?	1953
60	Ankle (R.)	1952	Rheumatoid arthritis, gout	1954

joints and have indicated the diagnosis made at the time, together with the date of onset of spinal symptoms which made the correct diagnosis possible.

I should like to stress the association of urethritis and joint involvement. Of our 5 cases of urethritis all had involvement of joints except 1. In 3 cases peripheral joints were involved and the manubrio-sternal joint in 1.

When urethritis and joint involvement occur at the same time the condition may be very difficult to distinguish from Reiter's syndrome. This diagnosis had been previously made in 2 of our cases. In fact, 1 patient had been diagnosed for years as Reiter's syndrome but an X-ray of the spine showed changes typical of spondylitis.

#### Chest Complications

The chest complications have been the subject of special study by Dudley Hart (1950) who found pulmonary symptoms in 74% of 60 patients, and by Mowbray and others (1949) who recorded symptoms in 25 out of 40 cases.

Pains across the chest, tightness of the chest wall, inability to take a deep breath and dyspnoea are common symptoms in spondylitics. They form almost an integral part of spondylitis and I have not classed such symptoms as complications. I have only selected those patients, 10 in all, in whom pulmonary symptoms were a major disability and in whom the added element of infection was present. These patients complained of cough and sputum in addition to the usual spondylitic chest symptoms, and added sounds were frequently encountered on examination. A history of acute pulmonary infection was very common in these patients—in fact, 1 patient had three attacks of pneumonia in three years, and 2 patients developed pneumonia in hospital. I have labelled this severe pulmonary condition, for want of a better term, as "bronchitis", though I am not at all certain that it is really the same thing as bronchitis as ordinarily encountered. The pulmonary expansion in all these patients was severely limited and in no case was it more than  $\frac{1}{2}$  in.

We have estimated the vital capacity in only a few patients and have found it to be considerably reduced. I do not know why some of our patients have developed these severe chest symptoms. It cannot be solely due to diminished respiratory movement because we have had many patients with only  $\frac{1}{2}$  in. chest expansion whose chests have given relatively little trouble. One factor, however, is apparent—it is largely in the older group that these symptoms develop. The average age of all our patients was 30.0 years, and in those with severe pulmonary symptoms 41.4 years.

Other chest conditions have been rarely encountered. One patient gave a history of hæmoptysis. Another suffered a pneumothorax first on one side and then on the other and subsequently developed bilateral pulmonary tuberculosis from which he died.

Pulmonary tuberculosis is not uncommon in spondylitics, and Dudley Hart (1950) has recorded 5 cases all developing tubercle after the onset of spondylitis. We have had only one other case of pulmonary tuberculosis which was discovered synchronously with a well-established spondylitis.

### Peptic Ulceration

Peptic ulcer is not uncommonly associated with spondylitis, but references to the association are rare. Mowbray and others (1949) encountered 2 ulcers in 27 cases. We have had 4 cases, and in all instances confirmatory evidence was obtained by a barium meal. Three of the ulcers were duodenal and one gastric. In 2 cases the ulcer symptoms appeared before the spondylitis, in 1 case afterwards, and in the remaining case spondylitis was detected in the course of treatment for ulcer.

One patient had a duodenal ulcer in 1948 and spondylitic symptoms appeared after an operation for ileostomy in 1950. He was severely anaemic when we admitted him in 1952 with gastric delay and a partial gastrectomy was performed.

Whatever is the cause of this curious association between peptic ulcer and spondylitis it considerably limits the possibility of adequate treatment. The use of deep X-rays must be considerably restricted and the employment of phenylbutazone, cortisone or ACTH is absolutely ruled out.

### Endocarditis

We have met with endocarditis in one case only, a patient who had aortic incompetence. Bywaters (1950), however, in discussing the occurrence of endocarditis in rheumatoid arthritis and allied diseases mentioned 4 cases of spondylitis in which valvular lesions were present.

Our case was a 45-year-old officer who had spondylitis since 1948. In 1949 he had an attack ofitis, signs of which were still present. There was no past history of rheumatic fever and no evidence of atheroma. The left ventricle was slightly enlarged and a well-marked aortic diastolic murmur was present. The mitral area was clear of murmurs. The blood pressure was 130/45 and the Wassermann reaction and Kahn tests were negative. The electrocardiogram showed left-sided dominance and the P-R interval was considerably increased.

### Disc Symptoms

Although many of our cases had been diagnosed as sciatica in the past we have not had any cases with lumbar disc protrusions. We have, however, had one patient in whom protrusion of a cervical disc produced quadriplegia.

This occurred in a 31-year-old soldier who had a rapidly advancing crippling form of spondylitis with a completely immobile neck and a bent head. Deep X-ray treatment, cortisone and Butazolidin in turn produced little benefit. He complained of paraesthesiae in both hands and a short while later had to be transferred to a neurosurgical unit as an emergency on account of a rapidly developing quadriplegia.

### Conclusion

In conclusion, I hope that our cases show that spondylitis is not a matter of backache only, and that some other incident may point the way to a diagnosis at an early stage.

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Dr. F. Dudley Hart:

### *The Treatment of Ankylosing Spondylitis*

The subject of ankylosing spondylitis has for years been of particular interest to me. Being a disease of young males it naturally comes to the fore in times of war and in peacetime the Services see more than their fair share of it because of the male age groups affected. In a series of cases analysed at Westminster some years ago (Hart *et al.*, 1949) we found that the average time between the appearance of symptoms and the making of the correct diagnosis was two years eleven months in Service cases, just over four years in civilian cases. This was shortly after the war; to-day the profession is more conscious of the existence of the condition and a correct diagnosis is made much sooner.

It is only possible in the time at my disposal to touch lightly on certain major aspects of therapy.

### *Activity and Rest*

Orthodox treatment before and during the war emphasized the importance of a good spinal position. Patients reclined in bed and in plaster cases which were gradually increased

in extension so that pain relief might run parallel with fusion of the spine in a good position. Such treatment has now been completely superseded by a more active approach to the subject. Swaim (1939) reported the results of the previous mode of therapy; they could hardly have been worse. Of 45 patients, 35 had completely fused spines, 31 had poor posture, chest expansion was poor in many, 20 had lost all hip movements and could hardly walk and 9 had died, mostly from chest infection. In our own series those unfortunately misdiagnosed as cases of spinal tuberculosis and treated by immobility show the worst end-results; in the vast majority hips are heavily involved. Swaim (1939) has now given up prolonged bed rest and spinal casts and uses only a light supporting walking jacket built high anteriorly over the rib margin and low posteriorly, so that the spine is held erect and inspiratory movements tend further to extend the spine. In these light jackets the patient's respiratory excursions are not reduced, but in the majority of spinal supports used in this disease in patients attending our unit for the first time, we have found that the vital capacity is diminished and full inspiratory excursions are prevented in greater or lesser degree. As a result of our findings we have entirely given up spinal supports, and a light support such as that advocated by Swaim which does not impede full respiration is the only one we would ever contemplate using and that rarely. Sharp and Easson (1954) in Manchester adopt the same procedure, rarely advising spinal supports as they have been unimpressed by their value either in preventing deformity or relieving pain. Wyatt (1945) also, as a result of his experience in the Ministry of Pensions, advocated mobilization and exercises and advised against the use of supports. While supports may prevent some deformity, the evidence that they do so is not impressive and we know of no series of patients treated with supporting jackets with a follow-up of ten years or more which has been compared with a similar series not so treated. A support is for a patient a constant reminder of his disability. Happily a bad jacket is usually rapidly discarded by the patient.

We have in our unit constantly advised patients with ankylosing spondylitis to maintain full mobility short of severe spinal strain from the start. We would prefer a spondylitic to have an active occupation rather than an indoor office post bent all day over a desk, for over and over again a patient has told us that he is better when active and worse when kept at rest. Awakening in the morning is often his worst time; after some hours of immobility in sleep he is stiff and in pain and takes anything up to two or three hours to become fully mobile. Some patients set the alarm clock to wake them at some hour in the night when they do a few simple exercises and then return to bed; in this way mornings are much better and their working day is easier. Other patients have also reported that they are better when their spines are gently agitated at night, as on moving vehicles, ships or aeroplanes, and that they then have no morning stiffness. We encourage full exercise and games which do not injure the spine such as swimming (not diving), golf and tennis. An active life with the normal daily or hourly overbreathing of simple exertion is better than set breathing exercises at set times, though these also we encourage. A patient with his disease confined to the spine is usually not crippled, but with his hips fused he certainly is, and fitness for work often depends entirely on presence or absence of hip involvement. A few weeks or months of bed or plaster shell rest may mark the beginning of progressive hip involvement.

Sharp and Easson (1954) have interesting data to offer regarding the dangers of immobilization. In their group of typical spondylitics, 19 had been at some time in the course of the disease immobilized in bed, plaster or on frames for periods of months or years. Of these 19, 5 were "virtual statues with rigid dorsal and lumbar spines and fixed or grossly limited hips, and two of them had practically fixed knees. Only 6 similar cases were encountered among the remaining 223 patients in the group". Patients so consistently tell this same story that we have now completely forsaken treatment by immobilization for a much more active regime.

#### Physiotherapy

In our opinion the most important item in physiotherapy is exercises and we do not ask more of our physiotherapists than for them to teach postural and breathing exercises and simple bodily movements which the patient should do regularly at home every day. Edstrom (1952) advises that for two or three periods a day the patient lies flat on boards with no pillow, the back in extension, and that back-stretching exercises be also done two to three times a day. We like our patients in hospital to have the freedom of the building and its grounds, and encourage simple physical training short of severe strain. Sonnenschein (1951) did not find ultrasonic wave therapy very effective in this disease and though a large variety of different physical methods have been advocated, none of them is dramatic in its effect though any may on occasion appear helpful. Various forms of applied heat are as likely to aggravate as to ease symptoms in this disease. The more advanced or crippled patient will often benefit from spa therapy, as will also a less advanced patient not severely incapacitated by pain.

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### Phenylbutazone

It has been widely claimed on the Continent that Butazolidin has antiphlogistic, antipyretic, analgesic and even antihistaminic properties. In the United Kingdom the general opinion is that while certainly an analgesic and antipyretic, its other properties cannot be demonstrated clinically in patients with established joint swelling. Its successful wide application in rheumatology to osteoarthritis, Paget's disease, rheumatoid arthritis and rheumatic fever and its use in malignant metastatic bony disease do not suggest that it has a particularly selective action and the fact that it helps the spondylitic in all stages of his painful disease also suggests that its benefit lies essentially in pain relief. A completely ankylosed subject still experiencing pain will frequently get more benefit from this drug than from any other. If the patient can tolerate the drug it is perhaps the most effective drug in the treatment of the advanced case. In daily doses of 200-400 mg. the male patient with advanced spondylitis usually tolerates phenylbutazone relatively well, but at this level of dosage the therapeutic effect may not be enough. Raising the dose to 600-800 mg. a day may produce symptomatic ease but will often be followed in time by gastric intolerance. Other toxic side-effects, such as oedema, skin rashes, buccal ulceration and defects in blood clotting are more rare and leucopenia and agranulocytosis rarer still. Gastric irritation is the main drawback, and we have seen cases where brisk hæmatemesis and melæna have occurred. Nevertheless, for the early painful and late fused but still painful case, phenylbutazone has much to offer. Pain is relieved and function thereby improved, though measurements of spinal range of movement in all but early cases remain unchanged. Holbrook (1953) found that after six months Butazolidin-treated patients did better than cortisone or corticotropin-treated ones; those patients doing well on Butazolidin after six months' therapy usually continued to do so over long periods, while cortisone or corticotropin had to be discontinued in many patients.

### Cortisone and Corticotropin (ACTH)

Continued long-term suppressive therapy of ankylosing spondylitis by cortisone and corticotropin has not found to date a great following in the United Kingdom. Most spondylitics though crippled and disabled to some degree are able to continue to lead a reasonable life and almost all of those attending our unit are at work. The well-known side-effects of these substances may cause trouble on continued therapy, particularly gastric upset. Nevertheless, in some patients continued suppressive therapy has proved its worth. Short-term therapy of the acute exacerbation is perhaps on the whole more popular.

In ankylosing spondylitis it is not unusual for the patient to complain of a short sharp exacerbation of symptoms, local or more generalized and lasting only one to four weeks. The pain may be severe over this short period and cause partial or complete crippling. Such an episode terminating naturally within a few weeks is rare in rheumatoid arthritis, where relapses usually last considerably longer. Cortisone or corticotropin is extremely useful in the treatment of this type of painful episode, and if natural remission has not commenced in ten to fourteen days it is our practice to start such therapy unless contra-indications (peptic ulceration or pulmonary tuberculosis) exist. Phenylbutazone is also helpful. Even in the acute exacerbation lasting a few days this form of treatment may be used if symptoms are prostrating.

We do not now use a dose of cortisone over 100 mg. a day, for if control is only adequate on this high dosage toxic side-effects may occur sooner or later if this dosage is continued. Some spondylitics are quite unaffected by a dosage under 100 mg. and in such cases it seems best to discontinue this form of therapy. Corticotropin is best reserved for short-term in-patient therapy.

### Deep X-ray Therapy

While the beneficial effects of cortisone, corticotropin and Butazolidin last only a few days after withdrawal of the drug, deep X-ray therapy frequently does not appear to produce amelioration in the clinical picture until towards the end or after the cessation of treatment.

In our unit we use 1,000-1,500 r skin dose, treatment being given only on alternate days to a given area. The routine procedure adopted by Dr. Allichin (Hart *et al.*, 1949) was to use X-rays of kV 180-200, filtration 1.5 mm. copper, half-value layer 1.7 mm. of copper, the skin dosage in each field never being more than 150 r in any one day. Treatment was not given to more than two fields daily, the period of therapy being spread over three to four weeks. The advantage of this smaller dosage and more localized application is that a further course can be given and systemic upset is much less; with the generalized semi-intensive method using 2,000 r total (skin) dosage further courses of therapy are not advisable. In addition to irradiation of the spine we have employed deep X-ray therapy in our unit in smaller dosage of a few hundred roentgens to painful and tender areas elsewhere, e.g. pelvic girdles, knees and feet, frequently with very satisfactory results. We use no fixed routine as to the number of areas treated and if only one area is causing symptoms we may

only treat this site. It is, however, not uncommon after treating a painful area in the spine to find that as the pain recedes in the area under treatment it appears in areas untreated. Care is taken, therefore, to ascertain that no signs or symptoms arise from other areas in the spine and if there is any doubt the entire spine is irradiated.

In our own experience the majority of patients obtain very definite relief from symptoms. This relief is not paralleled, except in very early cases, by marked improvement in range of spinal movements; relief from pain is more striking than relief from stiffness. Pain relief usually commences about half-way through the course of treatment and becomes maximal some weeks later; in our series the average time of maximal improvement was four weeks after cessation of therapy.

It is not known why deep X-ray therapy improves the patient; it is debatable whether it alters the natural course of the disease. In the majority of cases relief is obtained, but not in all. Such relief may last weeks, months or sometimes years. Whether deep X-ray treatment can bring on natural remission is still open to question. It is, however, the one form of treatment which usually gives symptomatic relief for a considerably longer period than the time of actual application of therapy.

What are the risks of deep X-ray treatment? Melæna and secondary anæmia do occur occasionally, particularly on therapy of 2,000 r and upwards, rarely on lower dosage. Van Swaay (1950, 1951) reported autopsy findings in 3 cases who died of myeloid leukaemia and he has since (1953) informed me of a further 4 cases which have come to his notice. Aplastic anæmia is rare; Sharp and Easson (1954) report such a case. Activation of quiescent pulmonary tuberculosis is another potential hazard. We know of no proven case of irradiation nephrosis at the low dosage used in this disease.

I have not touched on all branches of therapy; orthopædic surgery for instance has a part to play though a relatively small one except perhaps in the advanced case.

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Colonel W. Roy Ward:

#### Review of 93 Service Cases

A review has been made of 93 Service patients treated with deep X-rays at Mount Vernon Hospital for ankylosing spondylitis from 1945 to 1953 inclusive. Of these 93 cases, 30 were Army, 28 Royal Navy and 35 Royal Air Force.

During the same period the total number of all cases (i.e. with civilian cases) treated with deep X-rays for this condition was 300.

A recent follow-up of the Service cases shows that just over a third are well, just under a third are moderately well, three died of other causes not related in any way and approximately a quarter of the cases could not be traced. Of the 93 cases 17 had more than one course of deep X-rays. Table I shows the cases tabulated in greater detail.

TABLE I.—ANKYLOSING SPONDYLITIS. REVIEW OF 93 SERVICE CASES

Treatment year	Total	Result		Died	Lost	Further treatment
		Well	Moderately well			
1945	22	6	10	1	5	5
1946	18	7	6	1	4	3
1947	9	1	4	0	4	—
1948	15	5	5	0	5	3
1949	9	4	1	1	3	3
1950	2	2	0	0	0	1
1951	8	6	1	0	1	1
1952	6	4	1	0	1	—
1953	4	4	0	0	0	1
	93	39	28	3	23	17

## Section of Pathology

President—Professor L. P. GARROD, M.D., F.R.C.P.

[November 16, 1954]

### The Haemolytic Activity of Cold Antibodies

By J. V. DACIE, M.D., M.R.C.P.

*Department of Pathology (Haematology), Postgraduate Medical School of London*

FIVE years ago in a paper presented to the Section of Pathology of this Society I showed that cold antibodies that were generally considered to act as haemagglutinins only (agglutinating type of cold antibody) had in fact unexpected haemolytic properties. The cold antibodies I was then investigating were found in the sera of several patients who had recently suffered from virus pneumonia, and also at very high titre in the serum of an elderly subject who was suffering from a mild but chronic form of acquired haemolytic anaemia. The main facts that emerged from this study were as follows (Dacie, 1950): (a) normal erythrocytes underwent haemolysis if the serum-corpuscles suspensions were suitably acidified (optimum pH 6.5–7.0); (b) the haemolysin titres using normal erythrocytes were far less than the agglutinin titres; (c) complement was required for fixation of antibody in the cold as well as for lysis; and (d) paroxysmal nocturnal haemoglobinuria (PNH) corpuscles underwent haemolysis in far higher dilutions of the patients' sera than did normal erythrocytes.

These observations posed a number of problems and I shall try to deal with some of these in the present paper.

*The effect of pH on haemolysis.*—Are the antibodies always haemolytic and how constant is the effect of pH? I have by now investigated 15 different sera containing cold antibodies at high concentrations—in each instance the agglutinin titres exceeded 1024 at 2° C. Eight of the sera were from patients convalescing from virus pneumonia, and seven were from patients with chronic acquired haemolytic anaemia of the cold-antibody type. With all but one of the sera it was possible to demonstrate haemolysis of normal corpuscles. However, the ability of the antibodies to cause haemolysis was found to vary from serum to serum and the effect of pH was not entirely consistent. For instance, although acidification markedly increased the amount of haemolysis produced by the sera of 10 of these patients, in 1 patient with virus pneumonia and in 3 patients with chronic haemolytic anaemia a considerable amount of haemolysis was produced by unacidified serum, and acidification to pH 6.5–7.0 only slightly increased haemolysis. In Fig. 1 are shown the pH-haemolysis

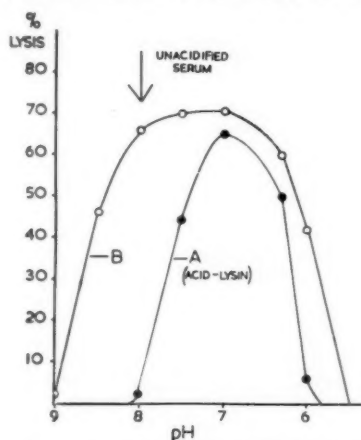


FIG. 1.—Effect of pH on the haemolysis of normal erythrocytes by two sera containing high-titre cold antibodies. Curve A: typical curve of an "acid-lysin"; Curve B: an exceptional curve showing almost maximal haemolysis in unacidified serum.

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curves obtained with the sera of two different patients suffering from the cold-antibody type of chronic acquired hæmolytic anæmia. Curve (A) is typical of an "acid-lysis"; there is little or no hæmolysis in undiluted serum (pH 8.0), maximum hæmolysis at pH 6.5 to 7.0, and inhibition below pH 6.0. Curve (B) was obtained with one of the exceptional sera which produced almost maximum hæmolysis when unacidified. The inhibition of hæmolysis which occurs at a pH below 6.0 seems due to inhibition of complement rather than to a failure to adsorb antibody (Fig. 2).

It is interesting to compare the effect of pH on other types of antibodies which cause lysis of erythrocytes. Variation of pH between 6.5 and 8.0 makes little difference to hæmolysis by anti-A or anti-B, and with antibodies of the Donath-Landsteiner (D-L) type, as found in paroxysmal cold hæmoglobinuria (FCH), the optimum pH seems typically to be in the region of 7.5 to 8.0, with acidification to a pH less than 7.5 diminishing rather than increasing hæmolysis. The curves in fact seem identical with those of the atypical sera containing high-titre agglutinating antibodies (curve B, Fig. 1 and Fig. 3).

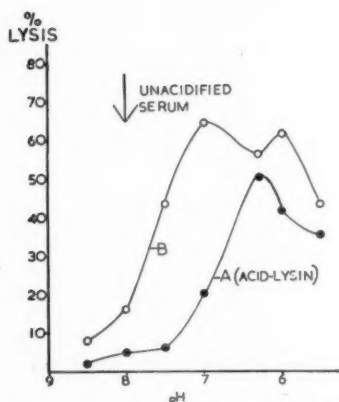


FIG. 2.—Effect of pH on the hæmolysis of normal erythrocytes by two sera containing high-titre cold antibodies. The experiment was carried out in two stages, sensitizing at 2° C. at different pH's and allowing hæmolysis to take place at a constant pH (same sera as in Fig. 1).

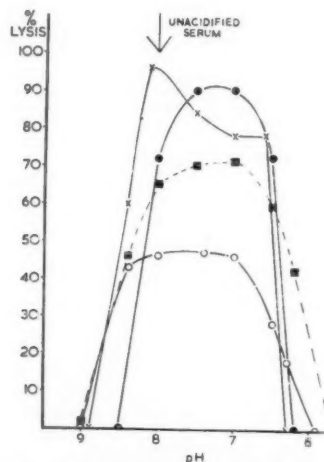


FIG. 3.—Comparison of the effect of pH on hæmolysis of normal erythrocytes by a serum containing high-titre cold antibodies (interrupted line) and three sera containing Donath-Landsteiner antibodies (continuous lines).

*Comparison between high-titre agglutinating cold antibodies and the Donath-Landsteiner antibody.*—I shall now refer to other points of similarity and dissimilarity between the antibodies which cause marked agglutination in the cold (as well as hæmolysis) and the Donath-Landsteiner (D-L) antibodies of PCH. As already mentioned, the effect of pH on the activity of the two types of antibody is usually, although not invariably, different—the optimum pH for the *in vitro* activity of the D-L antibody is pH 7.5 whilst in most instances of the other type the optimum lies between pH 6.5–7.0. There are, however, two rather distinct differences: (1) the D-L antibody seldom if ever seems to be found in anything like as high concentration as the agglutinating cold antibodies; (2) the D-L antibody is usually relatively far more hæmolytic to normal cells than is the agglutinating type of cold antibody—to put it another way, the hæmolysin titre of a D-L antibody using normal erythrocytes is close to the agglutinin titre, whereas with sera containing high-titre cold agglutinins the hæmolysin titre, using normal cells at optimum pH, is usually far less than the agglutinin titre. The agglutinin-hæmolysin titre relationship using several sera is illustrated in Table I.

Serum Da. was from a patient with chronic hæmolytic anæmia of the high-titre cold antibody type. She suffered from Raynaud's phenomena and was described as Case 3 by Ferriman *et al.* (1951). This serum contains cold antibodies at a very high concentration. The agglutinin titre was 128,000 at 2° C. and 8,000 at 18° C.; there was no agglutination at

TABLE I.—

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TABLE I.—DIFFERENCES IN THE ABILITY OF SERA CONTAINING COLD ANTIBODIES TO CAUSE HÆMOLYSIS.

		Serum Da.	Serum Fi.	Serum Ca.
Agglutinin titre	30° C.	<2	4	<2
	18° C.	8,000	2,000	8
(N cells in saline)	2° C.	128,000	8,000	32
Hæmolsin titre	30° C.	<2	4	<2
	18° C.	32	128	2
(N cells in acid-serum, pH 7.0)	2° C.–37° C.	<2	8	32
Hæmolsin titre	30° C.	64	512	<2
	18° C.	8,000	8,000	16
(PNH cells in serum, pH 8.0)	2° C.–37° C.	16,000	16,000	64

N cells = normal erythrocytes.

PNH cells = paroxysmal nocturnal hæmoglobinuria erythrocytes.

Titres were read after 2 hours at 18° C. or 30° C., or after 1 hour at 2° C. followed by 1 hour at 37° C.

30° C. The serum was, relatively, only weakly hæmolytic, the hæmolsin titre at 18° C. being 32 at pH 7.0. No lysis developed at 30° C. or if the cell-serum suspension was cooled at 2° C. before being warmed at 37° C. PNH erythrocytes were hæmolyzed at 18° C. to the same titre to which normal cells were agglutinated (8,000); the hæmolsin titre was 64 at 30° C.

Serum Fi. was from a patient who developed an acute hæmolytic episode following virus pneumonia. The cold-agglutinin titres at 2° C. (8,000) and at 18° C. (2,000) were substantially less than those obtained with the serum of the patient Da. However, the thermal range of the antibody extended higher than that of the patient Da., for agglutination took place at 30° C. (titre 4). The antibody, despite its lower agglutinin titre, was relatively more hæmolytic; the hæmolsin titre using normal corpuscles was 128 at 18° C. and 4 at 30° C. The hæmolsin titre using PNH corpuscles was moderately high (512) at 30° C.

Serum Ca. was from a child, probably suffering from congenital syphilis, with paroxysmal cold hæmoglobinuria. The behaviour of the antibody appeared to be that of a typical Donath-Landsteiner antibody. At 2° C. the agglutinin titre was quite low (32) but even so the antibody had an unusually high thermal activity, causing agglutination at 18° C. (titre 8). The hæmolsin titre using normal cells was close to the agglutinin titre—32 at 2° C., and 2 at 18° C. The hæmolsin titre using PNH cells was slightly increased to about twice the agglutinin titre.

*The role of complement.*—Complement is required for hæmolysis, but in addition both types of antibody—the high-titre agglutinating antibodies and the D-L antibodies—appear to be better adsorbed if complement, or fractions of complement, are present when the corpuscles are being sensitized. With both types of antibody it may be impossible to demonstrate hæmolysis if cells are sensitized at 2° C. (or 20° C.) in heat-inactivated serum, even if fresh normal serum is added when the suspension is subsequently warmed at 37° C.

There is no evidence that the antibodies are destroyed by heating at 56° C. for thirty minutes; rather it seems that, if components of complement are present, the antibody is bound on to erythrocytes firmly during sensitization in the cold, and that the effect of previous heating of the serum is to diminish the adhesion of antibody to cell surface so that elution takes place rapidly when the temperature is raised. Heating certainly does not prevent the adsorption of the antibody. This can be demonstrated with the Donath-Landsteiner antibody, as follows (Dacie, 1954): Normal corpuscles are sensitized in the patient's heated serum at 2° C. (Stage I); then washed in saline at 2° C. and finally resuspended in fresh normal human serum at 37° C. (Stage II). No hæmolysis develops. The cell-serum suspension is then rapidly centrifuged whilst still warm, the serum separated, and a further supply of normal corpuscles added to the serum. The suspension is then chilled at 2° C. (Stage III) and finally rewarmed at 37° C. (Stage IV). Hæmolysis develops. This is because hæmolytic antibody was in fact adsorbed from the heat-inactivated serum at Stage I and was eluted into the normal serum at Stage II.

The experiment described in the preceding paragraph was carried out using the D-L antibody. However, it is also easy to show that hæmolytic antibody is adsorbed from heat-inactivated serum containing high-titre agglutinating antibodies. This can be done by sensitizing normal corpuscles at 2° C. in fresh and in heat-inactivated patient's serum,

respectively, washing the sensitized corpuscles in saline at 2° C. and then allowing the antibodies to be eluted off into warm saline at 37° C. By titrating the warm-saline eluates with normal corpuscles and with PNH corpuscles it can be shown that both eluates—that made from corpuscles sensitized in patient's fresh serum and that made from corpuscles sensitized in patient's heat-inactivated serum—contain approximately the same concentrations of agglutinating and hæmolytic antibody.

The question as to whether the thermolabile components in serum which seem to affect the binding on of antibody in the cold are identical in all respects with the C'1 and C'2 fractions of complement has not yet been resolved. In 2 patients with FCH studied in America, Jordan, Pillimer and Dingle (1951) concluded that if the C'4 (stable) component was missing adsorption of antibody in the cold phase does not take place. In addition it seems clear that thermolabile components are also important in most instances—the observations of Jordan, Pillimer and Dingle suggest that the C'1 and C'2 fractions of complement may be interchangeable in this respect.

With the D-L antibody it is easy to show that when cold-sensitization of erythrocytes is allowed to take place complement (as tested for with sensitized sheep cells) is removed in significant amounts from the serum at a stage before hæmolysis is discernible. With the high-titre agglutinating antibodies it is less easy to demonstrate that complement is adsorbed when cells are sensitized at temperatures (e.g. 2 to 5° C.) sufficiently low to prevent hæmolysis. One reason for failure of fixation of complement at 2 to 5° C., and incidentally for the occasional failure of hæmolysis to take place on subsequent warming, may be that the very rapid agglutination that takes place at low temperatures inhibits complement adsorption. Alternatively, it may be caused by the concentration of antibody being far greater than is the case with the D-L antibodies. The results of actual experiments are shown in Tables II and III.

TABLE II.—ADSORPTION OF COMPLEMENT IN THE COLD PHASE OF SENSITIZATION

Serum	Complement content of serum after sensitization at 2-5° C. (units)	Control complement content (units)	Subsequent hæmolysis of sensitized normal erythrocytes
PCH I	3	35	+
" " II	18	110	+
High-titre agglutinating I	62	78	+
" " " II	70	96	++
" " " III	115	114	++
" " " IV	88	93	++
" " " V	73	92	+

PCH=paroxysmal cold hæmoglobinuria.

Normal erythrocytes were suspended in the patient's sera, the pH of which was adjusted with hydrochloric acid to the optimum for hæmolysis. The tubes were centrifuged after 1 hour at 2-5° C., and the complement content of the supernatants estimated as described by Dacie (1954). The control tubes contained saline in place of the erythrocyte suspension.

TABLE III.—UTILIZATION OF COMPLEMENT BY A HIGH-TITRE AGGLUTINATING ANTIBODY

Serum	pH	Temperature	Lysis	Complement content of supernatant serum (units)
Patient	6.5	37° C.	0	90
Control	6.5	37° C.		90
Patient	6.5	17° C.	++	8
Control	6.5	17° C.		110
Patient	8.0	17° C.	trace	70
Control	8.0	17° C.		110
Patient	6.5	2° C.	0	150
Control	6.5	2° C.		150

Normal erythrocytes were suspended in the patient's serum at different temperatures and pH for two hours. The complement content of the supernatant serum was estimated as described by Dacie (1954). The control tubes contained saline in place of the erythrocyte suspension.

Table II shows that in contrast to the clear-cut results obtained with the sera from the two cases of paroxysmal cold hæmoglobinuria (PCH I and II), little or no complement was removed from the serum by normal corpuscles sensitized at 2° C. in the 5 high-titre agglutinating antibodies (I-V), despite the fact that the cells subsequently underwent hæmolysis on warming.

Table III shows how the removal of complement from a single high-titre agglutinating serum was affected by the temperature and pH at which sensitization was allowed to take place. It was only at 17° C. that lysis and complement utilization occurred, and then only in really significant amounts in the acidified serum sample.

*Sensitization to antiglobulin serum.*—The cold antibodies under discussion sensitize cells to antiglobulin serum as well as causing agglutination and hæmolysis. A consideration of this phenomenon is beyond the scope of this paper. However, there is one point that should be made. This is that fresh serum is required in the cold sensitizing phase for the incomplete antibody to be retained on the cell surfaces when they are washed subsequently in warm saline. As with the hæmolytic reaction it seems as if antibody is readily adsorbed from heat-inactivated serum, and that the presence of complement prevents the rapid elution of antibody and this allows the antiglobulin reaction to be carried out. I have evidence that all four fractions of complement are required.

*Possible identity of agglutinating and hæmolytic antibodies.*—The last point to consider is whether the antibody which causes hæmolysis and that which causes agglutination are identical. Up till now I have avoided as far as possible the use of the terms hæmolysin and agglutinin. The evidence seems more in favour of these being a single antibody than the alternative, and suggests that differences in the relative agglutinin or hæmolysin titres of different sera are due to subtle differences in the antibody molecules, which affect the ability of the antibodies to cause adsorption of complement. There seems no question but that the antibodies I have been discussing are potentially hæmolytic, and it seems unlikely to be a coincidence that normal erythrocytes are agglutinated and PNH erythrocytes hæmolysed more often than not to about the same titres by most of these antibodies; it seems as if each type of cell reveals a different facet of antibody activity. This is also probably true of anti-A which agglutinates normal erythrocytes strongly and normally hæmolyses them only weakly. Anti-A hæmolyses PNH corpuscles to about the same titre that it agglutinates normal ones (Dacie, 1949).

*Practical demonstration of hæmolysis.*—Lastly, a few practical points in demonstrating hæmolysis by the high-titre agglutinating antibodies. It is important not to use too strong cell concentrations, for with concentrations greater than 4% there is a possibility of causing traumatic hæmolysis of strongly agglutinated cells (Stats, 1945). However, with a final concentration of cells of 1 to 2% there seems no risk of this.

Room temperature (about 18° to 22° C.) seems to be the optimum temperature for demonstrating hæmolysis. This is not too cold for complement lysis to proceed and is usually well within the thermal range of the antibodies. One final point, some of the sera containing cold antibodies in high concentrations are deficient in complement activity. In attempting to demonstrate lysis it is therefore important that serial dilutions of the patient's serum be made in fresh and acidified normal human serum before concluding that a serum lacks hæmolytic activity.

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## Section of Psychiatry

President—W. MAYER-GROSS, M.D., F.R.C.P.

[October 12, 1954]

### Clinical Research in Psychiatry: Retrospect and Prospect [Abridged]

#### PRESIDENT'S ADDRESS

By W. MAYER-GROSS, M.D., F.R.C.P.

This paper is an attempt to sum up the experiences of fifteen years as a research worker in a mental hospital remote from the seats of learning.

When I was appointed Director of Clinical Research at the Crichton Royal in 1939, the venture was to me both welcome and attractive. I had come from a teaching post in a German university, and had spent six years at the Maudsley Hospital in London: clinical research, that is, research into the causation of disease studied at the bedside, seemed a field very familiar to me. Scientific work in German teaching hospitals and clinics was to a large extent of the same kind; so much so that the concept of "clinical research" as a separate branch of study has never been formed and there is no corresponding phrase for it in German.

This is how I formulated my task at the time of my appointment: the lifting of daily clinical experience into the light of scientific investigation; looking for the unusual, illuminating case; testing scientific methods on clinical material; bringing theoretical problems to the patient's bedside; applying scientific critique to the therapeutic procedure; trying out new therapeutic methods under controlled conditions; collecting clinically well-studied case material for statistical elaboration and follow-up studies; instruction of young specialists in research methods.

In its typical English meaning, clinical science was first defined by Sir Thomas Lewis. His conception was closely connected with the method of teaching medicine in this country. Here the teacher is an eminent clinician chosen by the reputation of his wide experience and large practice; he teaches the art of diagnosis and his methods of therapy. He chooses as objects of his personal teaching all those important approaches and practices which the student cannot find in the printed texts, the imponderable, immeasurable and uncountable facts which the budding physician can pick up only at the bedside.

In Central Europe, on the other hand, the choice of teachers in the medical faculty was first of all influenced by their scientific achievements and by the recognition of their published work. The teaching of the professor in the Continental and Scandinavian medical school is consequently much more theoretical in the form of lectures and lecture-demonstrations, and he is expected to continue his research work. Medicine and science were in much closer contact and better integrated. This, probably, contributed to the prominent position of French medicine in the nineteenth century and to that of German medicine at a later period and up till the First World War.

However, the link-up of teaching and research had also less desirable consequences: it led to overloading of the curriculum with theory and science, to the production of medical literature *en masse*, to an excess of scientific or pseudoscientific writing and publication because the learned paper was the hall-mark of the highly qualified physician with academic aspirations. "The idea", to quote from Sir Thomas Lewis's remarks, "more prevalent perhaps in certain foreign countries than in our own, that research is a suitable introduction

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to general consulting practice, is not only intrinsically unsound, but has proved itself mischievous."

Lewis deliberately painted in black and white the contrast between the consultant and the research worker when in 1930 he first made his claim for clinical research. In his view preparation for success as a consultant on the one hand and for a career in clinical research on the other "present irreconcilable and deep-seated differences". The practising physician needs diagnostic ability, a "giant memory", "encyclopaedic knowledge", "clinical omniscience", his training is "too purely observational" to serve scientific study. Moreover, curative medicine deals with the individual, "progressive medicine is collective". Lewis goes so far as to insist that "the practice of medicine from its very nature is destructive to consecutive thought, it weakens the very power to think consecutively and therefore clearly..." Self-confidence is one of the essentials to the practice of medicine—while diffidence is an essential quality in investigation because it breeds inquiry.

If one wants to apply the idea of clinical research to psychiatry, one should be aware of these high claims of clinical science at the outset, even if Lewis's formulations may have been deliberately provoking at the time and are now somewhat out of date, at least for general medicine. It is noteworthy how little is made of the difference between research in the laboratory and research at the bedside. There Lewis saw no discrepancy that could be compared with the conflict between "samaritanism" and the "full solicitude for the sick" on the one hand, and the intensive study of cases in which manifestations are "deliberately sought or actually provoked" on the other.

Translated into the conditions of our own specialty, there was, and still is, little indication that the psychiatrist is too much concerned with diagnosis. If anything, there is too little diagnostic ability and interest among psychiatrists; diagnosis is belittled as fixing a label, "if you must"—although with the arrival of various physical treatment methods, diagnosis should be of the greatest practical importance. With the neglect of diagnosis goes, however, a bias towards casuistry: the emphasis put on the incomparability of the single case, the excessive preoccupation with individuals, the contempt for systematic observations of series and for statistical methods. In this respect, indeed, psychiatric practice fifteen years ago and to-day resembles that of general medicine twenty years ago and similarly challenges the efforts of the research worker. Without full clinical observation, without history and documentation in well-kept case records, clinical research into the course and causation of diseases, or into the mechanism underlying observed symptoms, is impossible. To know what to look for, but not be too absorbed to notice the unusual, is not easy to teach; but it was at this point that my first efforts began; with the willing co-operation of my colleagues it was slowly possible to build up the clinical material from which research could begin.

Meanwhile the curative practice of which Lewis contends that it "weakens the power to think consecutively", had taken full possession of psychiatry. Because of wartime shortages of staff and other emergencies, patients were rushed to physical treatments, some even without being adequately observed beforehand. The practising psychiatrist, for decades used to prudent contemplation on the effect of time on his patients, became extremely active in applying the new therapies at the first opportunity. And the research worker found new difficulties by resisting this hurried tendency to practical success.

While on the one hand this hyperactivity tended to hinder clinical observation and the study of the natural features of disease, the bold physical methods offered, on the other hand, a new and unexpected opportunity of experimental approach to psychiatric illness. Convulsions, hypoglycaemia, operations on the hemispheres and thalami, sleep and sleep-like states produced by gases or drugs with the idea of emotional relief and for the disclosure of subconscious contents, invited inquiries of many kinds. The therapies originally based on poorly disguised empiricism and their rationale seemed urgently in need of elucidation. A host of new questions was welling up while the treatments were applied and their mechanisms and side-effects studied in detail. Like so many others, we were attracted by this opportunity to study symptoms produced on physical procedures.

Hypoglycaemia especially seemed to offer the most welcome opportunity of investigating the carbohydrate metabolism in its relation to brain function. Here was also the proper use for our laboratory which would satisfy the medical superintendent's interest in biochemistry. Under a resourceful senior technician, we went in search of an answer to a few of the most urgent questions. Thanks to the special arrangement in Sakel's treatment whereby the same patient is treated daily over several weeks under identical conditions, the situation seemed unusually favourable for relatively exact studies. Young and physically healthy subjects were treated by a procedure which left little to be desired as an almost experimental set-up. Besides the analysis of certain primitive movements on which I reported to this Section in 1943 (*Proceedings*, 36, 343), and a study of speech disorders under hypoglycaemia,

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observations were carried out on the relation of the glucose level in the blood to that in the C.S.F., of body temperature in coma, and of circulating amino acids in hypoglycemia. Using blisters for the determination of the glucose content in tissue fluid we came nearer to an explanation of the riddle of the apparent independence of blood glucose and state of consciousness. A series of experiments on taste and selection of foods in mild hypoglycemia disclosed a depressed sensitivity of the human taste buds serving the self-regulation of carbohydrate intake.

Hypoglycemic coma seemed also to be a condition suited for testing the effect of glutamic acid on mental performance, after American workers had discovered its psychological activity. In fact, the administration of glutamic acid easily wakened the patient from his coma. The mechanism of this effect is still under debate and has gained some practical interest with the discovery that glutamic acid has the same action in hepatic coma and in delirium tremens.

Meduna's concept of "oneirophrenia" as a form of schizophrenia due to an abnormality of carbohydrate metabolism, had obvious connexion with the basic concepts of our own work. We repeated his investigations, but could not confirm his findings. Clinical observation and metabolic tests did not correspond in our material and the "anti-insulin factor" which Meduna discovered in his patients' urine has since proved to be present in a similar proportion of the normal general population.

Hypoglycemia as the model, representing a certain form of experimental psychosis, led us, after the end of World War II, back to earlier investigations of mescaline and similar drugs which produce psychological abnormalities. The discovery of the new "phantasticum", lysergic acid diethylamide, was a challenge for the biochemist as well as for the clinician. In a dose of a few hundreds of milligrammes taken internally it induces a psychosis-like condition, or at least symptoms such as depersonalization and derealization, visual illusions of movement and colour, and distortions of the body image. The minute dosage suggested that its mode of action was that of an anti-enzyme effect. This seemed to be confirmed by a rise of hexose monophosphate concentration we found in the blood; our recent, more detailed analysis of this finding makes it doubtful if this is the correct interpretation and perhaps we are dealing with a parallel effect, the connexion of which with the psychological phenomena is not as simple as it appeared originally.

The description of the sequence of these investigations in some detail has been given to illustrate certain lines of clinical research in psychiatry in which laboratory work played an important part. Much less needs to be said of studies carried out in the clinical field itself. I may, perhaps, mention a few topics: the establishing by experimental tests of the existence and duration of retrograde amnesia after electrically induced convulsions; a survey of the occupational distribution of mental illness among Army Officers treated in our Military Hospital during the last war; a study on the significance of neurotic traits in childhood. Their prevalence was compared between officer-patients in the Military Hospital, and a control group of healthy officers in a battalion billeted in the neighbouring district.

Field work of this kind among ordinary people who have never been in hospital nor come within the orbit of medicine at all, has, as Sir James Spence (1954) has pointed out, become an important and extending branch of clinical research in the wider sense. Based on similar investigations on the Continent and in Scandinavia and supported by an intelligent and versatile Psychiatric Social Worker, I ventured in 1946 into a mental health survey of a restricted rural area, comprising over 56,000 inhabitants, in the South of Scotland.

In the time of uncertainty and transition immediately after the war years, the worker and her survey were surprisingly well received by the population and supported by the authorities; thanks to the tact and skill of the Social Worker it was carried through without a serious hitch; but its full results could not be published and those which have become known have not been heeded to any extent by those who could act on them.

One can, of course, doubt if a survey of this kind can be listed as research proper. One may question if it does not belong to such activities as the keeping of a record library or of filing cards, concerned with the collecting of material on which more detailed research can be based. The survey has not provoked the detailed studies we had hoped; on the other hand its practical advantage in linking up the hospital with the surrounding catchment area, of freeing the asylum from its position of dread and isolation by showing interest in people at home, was obvious. This process has been further accelerated by the setting up of clinics for children and adults and by all the other changes introduced with the coming of the National Health Service from which psychiatric hospital practice in this country has profited so much.

Another type of work in which research borders on practice and is of doubtful scientific

status, is the follow-up study. With the arrival of the various physical treatment methods, nothing seemed to be more logical and indispensable than to assess the results of these varied activities. In a hospital receiving its patients from many rather distant regions, one had to content oneself with a follow-up by letter; but even this makeshift method can be developed to a high perfection if the right person is in charge of the inquiry. As long as it lasted, this work was most instructive and fruitful for clinician and research worker alike; but it came to an end with the main worker's departure. It should have been resumed recently, but no funds were available to support it.

During the last few years our laboratory branched out into the field of electrophysiology. As with many other hospitals, an electroencephalographic machine was the starting point; it was the only one in the district, needed for practical use, but not sufficiently occupied by routine work. It became part of the research department and its employment for research purposes was possible only if its highly sensitive equipment could be constantly controlled by a trained technician. There was no Department of Physics next door, as would be found in a University, nor even a skilled radio or electrical engineer within a radius of 70 miles. The obvious solution was to accommodate and equip an electronic workshop on the spot under an expert engineer. The willingness and generosity with which this was accomplished by the authorities cannot be too highly praised. The hope was that new apparatus for studies in electrophysiology and in all other branches where it was needed could be constructed on the site. The technological isolation of the Department, which had held up much work before, was thus overcome.

It is remarkable how much time it took to direct these efforts into the right channels. Only recently, after more than four years, has some steady and fruitful output of work begun to appear. This includes studies on the electrophysiological concomitants of progressive senile decay; and on the correlation between the frequency of certain wave forms and some basic personality features.

The general plan has been for the electrophysiologist to work in closest contact with the biochemist and to link up both in problems of clinical significance. A laboratory like ours seemed to be the ideal frame for such co-operation. The problems are numerous and the methods are at hand.

If slowness and delay in reaction to clinical problems may have been due to technical obstacles in the case of electrophysiology, this could not be claimed as an excuse for the Department of Psychological Research. For years the Department proved almost inaccessible to clinical questions of research, and seemed surrounded by a high wall of concepts and tests which did nothing to elucidate the obviously abnormal, quite apart from discovering nothing that the clinician had not known beforehand. This wall was only breached when the psychologist was taken as a partner and co-worker into the daily run of the ward, in closest contact with the patient and his treatment. It has still to be seen how much research will profit from this readjustment, but the signs are favourable.

Turning to the difficulties and disappointments of the solitary research worker, I shall not give the full list of my frustrations, but only mention some human aspects which are probably experienced by many in the same situation. I can only blame myself for not having been able to overcome these obstacles. It is probably characteristic of the scientist who has no exchange of views with equals working in the same field, that he is haunted from time to time by hesitation about his techniques and by doubts as to the competence and reliability of his co-workers. As Emerson expressed it "Uncertainty and loss of time are the nettles and tangling vines of the self-relying and self-directed". Eventually one gets over these nightmares and regains the confidence and trust in one's own good luck and judgment of personalities. Prejudices of others are more difficult to combat, especially those on human nature. The conviction is widespread that everything and all has its price, including ideas, honesty and goodwill, and can be provided by money; but it is hard to tolerate in the field of research. It is difficult to defend personality, originality and imagination against official qualifications and testimonials if they alone are considered as decisive on the person and his qualities. If the worker so selected does not yield the expected result, he has to be replaced—and so on, till the principle proves correct.

Even if this maxim is misapplied in all branches of research and, in fact, in any productive and creative work—it will be felt much more when the choice of workers from whom to draw is restricted by physical conditions: by a place of work which is isolated from the stream of life and civilization. Science applied to a young field such as psychiatry is in need of young workers and of the enthusiasm of young doctors. Even the most up-to-date equipment should not deceive us, as it deceived our predecessors before the First World War, that it can attract the best minds and replace the academic vivacity, conviviality and com-

petition which is to be found even in the smallest university or school of medicine as a natural by-product of the gathering of young minds.

Thus, it would be difficult for me to calculate the amount of time and effort spent with the sole purpose of attracting the right people as collaborators in research; to rouse and keep the interest of young psychiatrists in the work they had taken up; and to fill by adequate replacement the gaps left by those who tended away from the loneliness of country life. Prospects of promotion based on scientific research work are still almost unknown in our specialty and few recognize it as an asset if it does not receive the official stamp of a higher degree. Much as one may deplore the excess of pseudoscientific literature on the Continent, the idolatry of higher degrees can lead to misuse and stultify creative impulses to a considerable extent.

Before concluding at this point my "job analysis" of the clinical research worker, I must mention the help I derived from regular visits to London. The lack of an adequate library, the urgent need for advice and discussion in technical matters, and for encouragement were recurring features of my remote existence. All the undisturbed and restful contemplation of country life would have been ineffectual without these journeys to the Metropolis which were generously granted by the authorities; and without the unstinting help I was given by many friends and colleagues when I came.

From such minutiae in the life of the research worker it is not easy to see the bridge to the problems of research policy; but I hope to show that there are also connexions. With the Medical Research Council's White Paper "Clinical Research in Relation to the National Health Service" (1953) clinical research has come of age: "The growth of scientific knowledge has now progressed to the stage at which clinical research can be developed, with confidence, on a scale commensurate with the need." The pamphlet refers to medicine in general and does not mention any specialties; but most of the 18 Research Units financed by the Medical Research Council enumerated in its Appendix are, in fact, highly specialized units. One even touches psychiatry at a fringe, being the Occupational Adaptation Unit of the Maudsley Hospital. The Paper's main concern is the plea for more funds for clinical research, but also for central control of such research in almost all its aspects. Not only will the newly constituted Clinical Research Board have the full responsibility for expense and prestige of clinical research units financed by the M.R.C.; it will also supervise and advise the Ministry on Exchequer money spent on what the pamphlet calls "decentralized research" at the level of Regional Hospital Boards and Management Committees. All whole-time clinical research workers above the grade of senior registrar, in other words all Directors of Research, should be chosen or at least approved by the Central Board. "The Boards should be debarred from paying salaries for whole-time research workers, above the grade of senior registrar." It is only too obvious that the "measure" of decentralized research worth this name which this pamphlet allows, is relatively unimportant.

It is not for me to judge how far this further centralizing tendency, besides the repeated emphasis on university supervision, is desirable in other branches of medicine and surgery. For psychiatry, where I can claim some experience here and abroad, the extreme centralization of clinical research is deplorable because it endangers the few units still alive in various parts of the country and will, I am afraid, stifle the initiative of establishing new units.

Some points can be made in its favour: it may help to avoid much diletantism; the plodding-on of frustrated young workers in poorly equipped laboratories; the repetition of work not worth repeating. It will probably ascertain lines of research which cannot go wrong, thus avoiding efforts in a direction or by a method that has already led to an impasse or may not be entirely safe for yielding results. One can also wish and hope it will assure some continuity of psychiatric research, because the imaginative genius who sees a new phenomenon or establishes a new correlation cannot grow where there is not a number of workers doing the groundwork, removing obstacles and studying side-effects; a certain ritual of careful observation is unavoidable before an important discovery can be made. Continuity of this kind is impeded when the atmosphere is dominated by the whims of one superintendent or of one research worker who insists on going his solitary way with fanatical single-mindedness whatever the result may be.

But yet, there is something to be said, in a field having such large stretches of the unknown, for tolerating the almost monomaniac worker. It may be better to waste money on one idea and allow for its final disproof. Is it worth while to play for safety when there is the smallest chance of missing one of those scintillating starting points of scientific research (Spence, 1954)? Why should there not be here or there one of these hibernating laboratories which wait for the God of Spring?—who, of course, does not come at the order of a Central Body.

If there were fully-staffed and equipped Departments of Psychiatry at the medical schools

and universities as there are for other specialties, they would be the obvious centre for "decentralized" research. A number of the schools have not even established the chair of psychiatry as indicated in the Goodenough Report, and in those which have toed the line the professor, often a king without a realm, is fully occupied in overcoming the primary obstacles put in his way while building up his Department and in extracting from his colleagues the few hours in which he can teach his undergraduates. While the psychiatrist in the mental hospital is overwhelmed by too many patients, the professor suffers from the opposite complaint: he has half a dozen or at the best a dozen beds and has to find his patients for teaching and study elsewhere. Compared with Continental and Scandinavian Universities, this is a state of development that is fifty years or more behind the times.

If one wants to learn from the past, there is no question that the more important and successful research workers in psychiatry elsewhere have been in relation, positive or negative to University Departments: Freud, Wernicke, Wagner-Jauregg, Kraepelin, Bleuler, Gjessing, Moniz, Meduna and Sakel; they all lived within the orbit of a school of psychiatric teaching, joining it or fighting it, and many finally took up a professorship. As there were no such schools here, it was left to the initiative of superintendents, of Board of Control commissioners or even of laymen on Boards and Committees, to promote research and find support for those sporadic efforts which characterize the development of British psychiatry in the last forty years.

Whatever may be apposite for general medicine and other medical specialties, I think it is conclusive that psychiatry here is not ripe for the monopoly of the universities as suggested in the White Paper; nor for the centralization of clinical research by which the "national" effort is supervised from one point only. There is need for the central Research Institute carrying out the fundamental work and where the periphery can go for advice and help; this was the function of Kraepelin's Research Institute at Munich. He would never have attempted to run the work in the periphery only on the Institute's lines. He was liberal and magnanimous and approved of the multifarious endeavours of other workers. In spite of all the trials and tribulations which I have truthfully described, I am convinced that they were worth while: my plea is for independence to be granted and preserved for the provincial worker, for generosity and for giving him the reins.

I would not have satisfied the theme of my address without a short preview of those problems which I think at present worth attacking in clinical research. I have already spoken of the promising co-operation between biochemistry and electrophysiology of the brain. If the chemist and physiologist could be joined by a neurosurgeon as well as by a clinician results could be expected in a foreseeable time. My second choice of combination would be that of pharmacologist and biochemist who should approach similar problems from another angle. There is much work under way in this field across the Atlantic and in this country. The addition of a chemical histologist and a physicist would round up the team which, however, needs the clinician to hold it together.

Closer to the clinical field and independent of laboratory equipment are studies on family life, on social group formation and stratification, especially in our crowded towns. They are ready to be started, with the modern sampling methods. Their first target might be psychological maladaptations, subnormals and other psychiatric casualties, of whom so many live in the community, with a doubtful influence on the atmosphere in which the healthy members of the family have to exist and in which children are reared and grow up.

A similar topic can be approached from a different angle: for those who feel as I do that this century's contribution to the industrial and mechanized age should be to humanize our modes of work and living, states of semi-invalidism belonging to the considerable fringe between health and disease are of great interest. Many ex-patients of our mental hospitals and clinics are in such a state after discharge; in fact, if we include chronic neurotics and somatic states with a psychological superstructure, psychiatry probably produces more subclinical abnormal conditions than any other part of medicine. It seems the obvious task for every mental hospital to collect data about the adjustment of former patients in the community and improve our effort of rehabilitation on the basis of such a follow-up. It may even pay to have a flying squad consisting of a doctor and a social worker, as Eugen Bleuler had in Zurich, which combines this research with monthly visits to the discharged patient and helps him to settle in his home.

Semi-invalidism among the elderly is discussed a great deal at present and studied too little. Without psychiatric assessment, all studies of illness of old age can be of restricted value only. A large number of these patients are now in the hands of the psychiatrists. Their personal data and histories alone correlated with their mental condition should yield an important contribution to the welfare of ageing people among whom we live; but I know of only one worker who recently approached this group. Many more are needed

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who, with an unbiased mind, give us its natural history, or try to collect data to prevent this disaster of many old people.

Prevention, of course, should be the ultimate aim of all research in disease; it has, however, a very different meaning if it refers to a neurotic deviation or to a case of senile dementia or of schizophrenia. According to certain fashionable hypotheses, for example, nothing could be easier than the prevention of neurosis or even psychosis by the proper upbringing of children, education of mothers in the principles of motherly care, closer family ties and household coherence. After my travels to India two years ago where I found inner coherence and love in the family exceeding by far any ideal painted by certain writers, but nevertheless a good proportion of neurosis of all types, both among adults and children, I became somewhat doubtful of these doctrines. However, the supposed influence of Western civilization on psychiatric illness, the hypothesis of the critical years in child development, the environmental contributory factors, undoubtedly present even in such a mainly constitutional illness as schizophrenia, deserve fresh study and assessment in a setting in which research is combined with remedial treatment.

Finally, another topic in which observation and controlled studies should replace armchair interpretation, wishful thinking and premature theorizing, is the psychology of the group and its application in therapy. Our times have seen the misuse of the group spirit on an unprecedented scale and more suffering and degradation have been due to the psychological forces in the setting of the masses than have been seen for a long time in history. If we could tame some of these forces and reduce them to subjection for purposes of therapy, we could probably dispose of many physical treatments and certainly dismiss prolonged psychoanalysis. Spontaneous group formation among the people outside and inside our hospitals deserves the attention of psychologists and sociologists who wear no blinkers; experimentation in this field could learn more from the behaviour physiologists such as Lorentz and Tinbergen than from Le Bon and Margaret Mead.

#### SUMMARY

I have tried to find out how far clinical research can be applied to psychiatry. I have done this not by discussing principles, but by describing the modest achievements of one worker over a period of fifteen years, and the difficulties and disappointments he experienced in spite of external circumstances which could hardly have been more favourable. In the light of these experiences, recent official declarations on clinical research had to be considered and it was seen how little these declarations took account of the special application to psychiatry. What I would suggest as a comfort in this situation is that the abundance of problems amidst the clinician's daily tasks seem to be much more capable of solution now than fifteen years ago; but it is essential that we have men and the means to tackle them.

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## BOOK REVIEWS

**Congenital Syphilis.** By David Nabarro, M.D., F.R.C.P. (Pp. xi+470; illustrated. 50s.) London: Edward Arnold Ltd. 1954.

The incidence of congenital syphilis in this country now stands at a record low level and a generation of doctors, including some venereologists, has arisen which have little or no acquaintance with this phase of the disease. The appearance of a book on the subject is thus timely and the author, a widely read worker, who between the two wars dealt with over a thousand cases of syphilis in children and infants at the Hospital for Sick Children, Great Ormond Street, has produced an interesting and readable monograph in which all aspects of the disease are carefully considered. As his twenty-three years' experience ended fifteen years ago, the work is inevitably a "period piece" and it is evident that some of his views are influenced by the writings of the famous syphilologists of the nineteenth century. It is well, none the less, to be reminded of the work of these pioneers and the collection of references at the end of each chapter is most valuable, especially to those who are tempted to believe that they are making an original observation.

Rather too much attention is perhaps paid to the traditional French concept of occult or parasyphilis, i.e. invasion of the foetus by the syphilitic toxin as distinct from true treponemal infection, though other controversial subjects such as third generation infection and congenital cardiovascular syphilis are, on the whole, judiciously dealt with.

It is not surprising that Dr. Nabarro is not at home with antibiotics, but he is less "penicillin resistant" than many of his contemporaries and he generously admits that, in adequate dosage, penicillin could doubtless take the place of metallothérapie.

The many case histories quoted make especially interesting reading and the whole work has been obviously been a labour of love. Though the photography is rather dated the book is beautifully produced and should be read and kept for reference by practising venereologists.

**Fluid Balance in Surgical Practice.** By L. P. Le Quesne, M.A., B.Ch., F.R.C.S. (Pp. vii+130; 41 illustrations. 17s. 6d.) London: Lloyd-Luke (Medical Books) Ltd. 1954.

It is probably true to say that the perfection of manual skill in surgery was reached at the beginning of the present century. By 1910, the main outlines of surgery as we know it to-day had already been laid down.<sup>1</sup> But the First World War fostered a great advance in surgical thought, with a special emphasis on physiological principles. Blood transfusion was introduced just before the war, but remained little more than a curiosity at the time. The continuous administration of fluids, tried soon after, made no great headway at first. The introduction, by Marriott and Keckwick in 1935, of continuous transfusion in amounts graded to the needs of the patient was the beginning, in this country, of the growth of transfusion services that underwent such acceleration during the Second World War.

Mr. L. P. Le Quesne, Assistant Director of the Department of Surgical Studies, Middlesex Hospital, London, is a surgeon who has grown up with these developments as part of his academic background. This book, which is based on the Moynihan Prize Essay for 1953, discusses the theoretical background to fluid and electrolyte exchanges, and describes practical problems concerning their control, as they arise in clinical surgery. Much of the illustrative matter is based on Mr. Le Quesne's own observations, and the book includes an appendix of annotated case histories, illustrating the management of various derangements of fluid balance.

The first chapter, entitled Physiological Considerations, considers first the units of measurements, and illustrates the value of expressing the concentration of electrolytes in terms of milli-equivalents per litre instead of mg. per 100 ml. A list of factors for converting a measurement in one unitage to one in the other is given. Diagrams illustrating the normal distribution and compartments of the body fluids are clear, and the discussion of normal intake and output of electrolytes and water is lucid. The second chapter considers the effects of operation on water and electrolyte balance, including the aetiology of post-operative salt and water retention. Administration of fluid and electrolytes in the uncomplicated case and in dehydration is then considered, and the question of potassium deficiency discussed. The subsequent chapters deal with renal failure and anuria; effects of excess water and salt; nitrogen and caloric problems; fluid balance in children; and technical considerations.

In these discussions the distribution of water and electrolytes within the body is assumed to be determined by the establishment of physical equilibria and no account is taken of steady-state conditions and other more dynamic aspects of body-fluid distribution and composition. But the theoretical background adopted is quite proper to the problems considered. The author puts forward the view that post-operative disturbances of water and salt metabolism result from the interaction of three factors: the secretion of posterior

<sup>1</sup>Ogilvie, W. H. (1954) *Brit. med. J.*, ii, 1435.

pituitary antidiuretic hormone, renal hemodynamic factors, and the secretion of adrenocortical salt-retaining hormones. Of these, the first and the third are, the author believes, by far the most important and what happens to salt and water balance during the post-operative period is, in his view, largely determined by the relationship between these two. He suggests that if the release of the antidiuretic hormone is only short-lived and that of the salt-retaining corticoids delayed in onset, the salt which is retained on the day of operation will on the day after operation be excreted, with diuresis, while salt and water retention will occur during the day after that. The pattern will therefore be one of separated retention. If, on the other hand, the secretion of antidiuretic hormone lasts until the day after operation and there is an overlap with the secretion of salt-retaining corticoids, then on the day after operation a pronounced diuresis will not occur, and the pattern of sodium retention will be distinct or coalescent. Unfortunately at present no direct evidence is adduced for this interesting hypothesis, which does, however, provide a ready explanation of much of what is seen in practice.

With the use of intravenous replacement has come the need to study the maintenance of the patient over long periods of time by means of intravenous ailments. Full consideration of these aspects lies beyond the scope of the volume under review but they are lightly touched upon, and the big problem of the negative nitrogen balance in patients maintained on intravenous electrolyte solutions and 5% glucose, is briefly discussed.

The book is well illustrated with clear diagrams, into the construction of which much thought has clearly gone. The writing is on the whole satisfactory, though occasionally the construction of the sentences makes the reading a little hesitant. The index is satisfactory and the production is good.

In the words of Thomas Gale (1586) "The restoring of that which is lost, is properly the office of nature, as to engender flesh, blood, and such lyke partes as are to be engendered. Notwithstanding the chirurgion herein is nature's minister." To the surgical ministers of nature Mr. Le Quesne's book is to be recommended, and particularly to those whose knowledge of modern ideas and practice with respect to fluid balance needs adding to or bringing up to date.

**Dental and Oral X-ray Diagnosis.** By A. C. W. Hutchinson, D.D.S., M.D.S., F.D.S., F.R.S.E. (Pp. xii+524; 946 illustrations. 75s.) Edinburgh and London: E. & S. Livingstone Ltd. 1954.

The main purpose of this book is to deal with the radiological aspects of diseases that affect the teeth and jaws. The first two chapters deal with normal radiographic anatomy. Radiographic technique is outside the scope of the book.

Professor Hutchinson has obviously an excellent source of material at his disposal for his book is lavishly illustrated with a wide variety of very good and interesting radiographs all of which are reproduced in facsimile, that is, whites and blacks have not been reversed. The quality of reproduction is worthy of high praise, praise to be shared by author and publisher and their technical assistants.

From his remarks in the preface it is clear that Professor Hutchinson believes that radiology cannot be dealt with in isolation from, and in practice must not be divorced from, clinical examination and other techniques used in diagnosis. No doubt for these reasons a large part of the text is devoted to a lengthy consideration of aetiology and clinical appearances, to such an extent that much of the book resembles the traditional type of textbook of oral pathology, though with radiographs substituted for the usual figures illustrating histology and clinical features; a resemblance which is emphasized by the mode of presentation and the authorities quoted. In a book of this size it is reasonable to expect to find discussed the minutiae of radiological diagnosis. What is the radiopaque fluid of choice for sialography and how long is it necessary to wait for it to be eliminated so that the other side can be radiographed without superimposition of shadows? How does one set about distinguishing an incisive canal cyst from a large incisive fossa? Can bone destruction due to invasion by a carcinoma be distinguished radiographically from that due to infection? The reviewer has sought in vain for answers to these practical questions that arise in oral diagnosis.

Radiography is a means of studying morbid anatomy in the living and the radiograph provides at a different level of resolution the same sort of information as is provided by histological examination. Wherever possible the radiologist must check his findings with those made by the pathologist and clinician or surgeon at operation. Statements regarding radiographic appearances are only convincing if supported by observations of this kind. From this point of view the book is in general disappointing. A number of statements that are expressed dogmatically are in fact open to question; for instance, is there any real evidence that "the most frequent cause of clicking temporomandibular joint is rupture of the attachment of the lateral pterygoid muscle to the disc"? It would perhaps be true to say that the

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application of heat may contribute to the spread of infection in osteomyelitis but it would be difficult to vindicate the statement that "one of the most common causes of (spread of pus in the spongiosa) is the injudicious application of heat before the pus has broken through the bone". There are furthermore a number of careless expressions which the critical reader will find irritating—"freak of growth", "hypotonicity of the sympathetics", and "alveolus" where the alveolar process is meant. "Harmless" is not a semantic substitute for benignity when used in connexion with neoplasia.

To summarize, in the reviewer's opinion the outstanding merit of this book is provided by the radiographs with which it is illustrated; both students and practising clinicians will profit from examining them. The type of practitioner for whom this book will perhaps have the strongest appeal is the general radiologist who at least occasionally has to give an opinion on radiographs of teeth and jaws.

**A Synopsis of Medicine.** By Sir Henry Tidy, K.B.E., M.A., M.D., B.Ch., F.R.C.P. 10th edition. (Pp xix+1253. 35s.) Bristol: John Wright & Sons Ltd. 1954.

The familiar green cover of this book, seen on a large number of bookshelves, bears testimony to its general usefulness and to the number of doctors who find it really helpful. Medicine is not a subject that allows itself to be presented in the form of a synopsis, and the feat of doing so in a manner so widely acceptable was achieved by the author nearly twenty-five years ago. The continued success of this book depends in no small measure on the remarkable amount of reliable information it contains and the ease with which it can be found.

This present and 10th edition has been thoroughly revised. Old wood has been discarded and new conceptions and advances included. "Look it up in Tidy" has long been a familiar phrase on the lips of students and qualified practitioners alike, and this 10th edition will ensure that these words will continue to be used in the years to come.

**Diseases of the Nervous System.** By Sir Francis M. R. Walshe, M.D., D.Sc., F.R.S. 8th edition. (Pp. xvi+357; 58 illustrations. 24s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

Many and varied are the motives which promote a young author to write a textbook for the benefit of practitioners and medical students. Some of them derive primarily from a youthful and almost naive discovery of the delights of his subject-matter—an experience which he cannot resist sharing with his juniors. But every now and again an older and more learned teacher turns aside from the hurly-burly of his clinic to impart the fruits of his experience to his disciples. In such cases we expect to find something different from the usual stock manual of information. We expect to find a more realistic presentation, wherein facts are sifted according to their value, and not tumbled together higgledy-piggledy fashion. The student will, it is hoped, be offered a truly balanced diet, and not an indigestible pot-luck. Certainly all these benefits are to be met with in Walshe's little book, now flourishing in the maturity of its 8th edition. It was a good thing that Walshe did not, in 1940, choose to remain silent upon a peak in Darien surveying the broad waters of neurology. Many batches of senior students would have been so much the poorer without the guidance of this little volume. By ruthlessly pruning away from his text the dead wood of neurological curiosities; by a strict and even ascetic observance of simplicity, dignity and force, Walshe has shown himself to be an artist as well as a scientist. His narrative is never dull: often arresting; sometimes provocative. Indeed the sole criticism that even the most captious colleague could venture is to wish that there were fewer evidences of a doctrinaire approach, fewer bees in the bonnet. But the textbook would not be the same without these personal touches—without which indeed no textbook can ever attain great stature.

Walshe's handbook makes easy reading. The text is elegantly written, tempting one to dip deeper, after having looked up and confirmed a specific point. British neurology is fortunate indeed in having such a distinguished textbook available for students and practitioners.

**Demonstrations of Physical Signs in Clinical Surgery.** By Hamilton Bailey, F.R.C.S., A.C.S., F.R.S.E., assisted by Allan Clain, M.B., F.R.C.S. 12th edition. (Pp. xii+456; 681 illustrations, many in colour. 38s. 6d.) Bristol: John Wright & Sons Ltd. 1954.

The stimulation of visual memory is an important method of teaching in many branches of learning, but in none more so than in clinical medicine and surgery. This approach is utilized to the full in this book, and its great and continued success is proof of the truth of the premises on which it was originally based.

This is a book that gives pleasure as well as an abundance of information. There is æsthetic satisfaction in turning its high quality pages and admiring the beautifully produced

illustrations. A feeling of time well spent is derived from the realization that all is laid before one with simplicity and clarity, and that each line and illustration makes its point and is easily understood.

When so much is offered it is inevitable that there should be minor criticisms, one being that the very excellence of the illustrations perpetuates the fallacy that there are significant clinical types of obesity, whereas adipose tissue is only deposited in the areas where fatty tissue already exists.

This book cannot fail to stimulate the desire in anyone who reads it to become a master clinician, and in this alone it does invaluable service.

To the individual it will give pleasure as well as much information, and those who possess previous editions well worn by constant reference will welcome this new one, replete as it is with new information and revision.

**The Brompton Hospital: The Story of a Great Adventure.** By Maurice Davidson, M.A., D.M., F.R.C.P., and F. G. Rouvray, O.B.E. (Pp. viii+152; 31 illustrations. 21s.) London: Lloyd-Luke (Medical Books) Ltd. 1954.

This story of the Brompton Hospital is written in a graceful style and is extremely well produced. The history of the institution itself is interspersed with lively sketches of physicians and surgeons who served there and with descriptions of the many activities in and about the hospital in Victorian England. This combination of the stories of both the hospital and of the staff shows how the spirit, tradition and pre-eminent reputation of the Brompton were created by the labours of those who worked for the hospital. The book is to be recommended highly both to the profession and to the lay public.

**Blood Groups in Man.** By R. R. Race, Ph.D., M.R.C.S., F.R.S., and Ruth Sanger, Ph.D., B.Sc. 2nd edition. (Pp. xvi+400; 34 illustrations. 30s.) Oxford: Blackwell Scientific Publications. 1954.

Since the first edition of this work in 1950, the number of known blood groups has increased and much new work has emerged from this field, particularly in relation to genetics and medicine. The authors have sensibly produced a new edition adding to the original text and including two new chapters; one on the Kidd group, the other on gene linkage.

The book begins with a useful introductory chapter covering some of the elements of genetics, and some further aspects of this subject are developed in a later chapter. The A,B,O; M,N,S and P blood groups are then described in some detail. The authors have played such a significant part in the evolution of knowledge about these subjects that they have been able to treat these chapters authoritatively and fortunately have retained unusual perspective in weaving their way through so many isolated facts. Those aspects of which the authors have no practical experience, such as the chemistry of antigens and antibodies, are cut perhaps unfortunately short.

There follows a detailed analysis of the Rh system in three chapters, followed by accounts of the Lutheran, Kell, Lewis, Duffy and Kidd groups. Since the Rh system plays such an important role in medical practice, one feels that there should be more than just the briefest mention of this aspect.

The book concludes with a short account of some very rare blood groups and two useful chapters on the laboratory aspects of blood grouping, followed by a summary of genetics and statistics. At the end of each chapter there is a searching bibliography.

Whilst this book can be highly recommended, it must be done so mainly for the specialist in the blood-group field. It is sufficiently comprehensive to prove an excellent work of reference.

**The Distribution of the Human Blood Groups.** By A. E. Mourant, M.A., D.Phil., D.M. (Pp. xxi+438; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1954.

This highly specialized book is committed largely to the spheres of the student anthropologist and the research worker in blood groups. It was printed as a companion to Race and Sanger's "Blood Groups in Man" and as such, is a useful extension of this subject in a limited field. A fundamental knowledge about genetics is presumed by the author and the reader is plunged early into the complexities of this subject.

The introduction, headed "The Application of Mendelian Characters to Anthropology", does scant justice to this aspect and here a discussion of genetic principles would make this book readable to more people. There follow five accurate and comprehensive chapters relating to characteristics of human blood groups, accompanied by a useful table for correlating the various terminologies which have developed around this subject. Throughout the book Fisher's nomenclature is used.

The account of various genetic characters which are of value in anthropological surveys

could be improved by including relevant features of amino-aciduria, particularly cystinuria, since there has been much work on the genetic distribution of these disorders.

Seven chapters comprise a detailed review of the distribution of all investigated blood groups throughout the various races of the world. The subject is treated in a scholarly way with careful consideration of the mixing of races and the movements of populations. The details of these chapters are well summarized in a series of excellent maps and it is amusing to speculate why the blood groups A and B are arranged in order of maximum incidence on either side of the "Iron Curtain".

There follows a useful and accurate chapter on blood groups in animals, particularly of value to workers studying problems in this hematological field. An attempt to synthesize the underlying factors influencing the distribution of blood groups around the world is interesting. The theory of selection is attractive, but little is said in this connexion about the similarity between some blood group antigens and bacterial antigens and their relative ability to stimulate the production of similar antibodies.

The book ends with a good chapter on the calculation of gene frequencies and some notes on relevant recent advances. A most commendable feature is a thoroughly comprehensive bibliography and an exhaustive series of charts and tables summarizing blood-group frequencies in different populations.

In its limited and specialized field this is a good book, but it is too technical to commend itself to those who are not closely allied to the subject.

**Multiple Sclerosis.** By Douglas McAlpine, M.D., F.R.C.P., Nigel D. Compston, M.A., M.D., M.R.C.P., and Charles E. Lumsden, M.D. (Pp. viii+304; illustrated. 35s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

This book has many excellent features. Throughout the authors show their wide experience and thoroughness. For those in search of the historical, geographical, aetiological and clinical facts of the disease, nothing is lacking. Each chapter is supported by a full list of references. The chapters by Dr. Charles Lumsden on the pathology of multiple sclerosis and other demyelinating diseases form an important basis for future study of the subject.

However, in a monograph about this dreadful disease, well recognized for a hundred years, physicians and patients will look for a bold statement of principles suggesting the possibility of a cure, or at least a determined attack upon the disease. In this book the social problem "can be briefly considered" in a single page. We are not told that multiple sclerosis, among other diseases, is a disgrace to society and that it could be broken by a determined social effort. It is time that somebody made this clear. Such a statement would have its greatest force if it were the theme of a book like this.

**Porphyrias: Their Biological and Chemical Importance.** By A. Vannotti. Translated by C. Rimington. (Pp. 258+xv. 50s.) London: Hilger & Watts Ltd. 1954.

In the first chapter, an account is given of the physico-chemical properties of the porphyrins. The older literature is critically reviewed, and considering the rate at which fresh evidence is being produced by the use of modern weapons (isotopes, chromatography, &c.) this chapter is well up to date. The next chapter gives methods of extraction and identification in sufficient detail to enable a well-equipped clinical laboratory to identify most porphyrins likely to be encountered. The third section deals with porphyrins in nature. Porphyrins occur in animal, vegetable and mineral sources, but the finding of porphyrin in a mineral would appear to indicate a previous animal or vegetable origin. From egg-shells to feathers, and yeasts to tomatoes, porphyrins seem very widely spread.

Next the role of porphyrins in human physiology is presented in considerable detail, and the modern theories of the place of series 1 and series 3 porphyrins discussed. The next chapter on changes of porphyrin metabolism in pathological conditions is very complete and valuable. It deals with the many causes other than the porphyrias for increased excretion of porphyrins. This chapter is followed by one dealing with the biological action of porphyrin and it is shown that apart from the much discussed photosensitizing effect, porphyrins in excess in the blood are capable of causing many of the symptoms of porphyria, such as the alimentary disturbances.

The chapter which follows on porphyria is particularly valuable owing to the many critically studied cases reviewed both from the literature and the author's own experience, and the reader is left to decide for himself the validity of the various classifications that have been made by various writers.

In the final chapter on treatment, while acknowledging the lack of any method of altering the fundamental disturbance of metabolism which occurs in porphyria the author gives so good an account of what steps can be taken to deal with these unfortunate patients, that one no longer has a feeling of complete therapeutic frustration when considering the porphyrias.

This is a delightful book to read. It is well written, and so well translated that only once did one realize that it had not been written originally in English. The fact that the translator is also an authority on porphyryns has added much to the up-to-dateness of the book, as the various translator's footnotes indicate. The only criticism is the brevity of the index. To balance this, there is a very complete bibliography for each chapter, collected together at the end of the book.

**Ancient Therapeutic Arts.** By William Brockbank, M.A., M.D., F.R.C.P. (Pp. 162; illustrated. 25s.) London: William Heinemann Medical Books Ltd. 1954.

This volume, one of the publishers' series of books on Medical History, publishes in book form the Fitzpatrick Lectures delivered by the author at the Royal College of Physicians in 1950-51. There are four lectures, described on the contents page as dealing with the Ancient Arts of Enema Administration, Cupping and Leeching and Counter-irritation, and The Less Ancient Art of Intravenous Injection of Drugs.

These essays make fascinating reading. The first of Enema Administration traces the history of this therapeutic art from the earliest known reference in the Ebers papyrus about 1500 B.C. to modern times. So continuous and so universal has been the practice of this art through the centuries that references to and quotations from the works of many of the great names in medical history appear in the text—Hippocrates, Galen, Celsus, the great Arabian physicians, the medieval Europeans including our own John of Arderne in the fourteenth century, Ambroise Paré, de Graaf and many in more modern times in the eighteenth and nineteenth centuries. The author describes fully the many purposes to which the enema has been put and the very varied ingredients, from the honey and oil and butter of the earliest times to strange mixtures, and even tobacco smoke enemata were used to resuscitate persons apparently drowned down to the beginning of the nineteenth century. The different forms of apparatus used for the administration of the enema are fully described and lavishly illustrated by the reproduction of original illustrations from the Middle Ages onwards. The enema in literature is dealt with by quotations from Burton's *Anatomy of Melancholy*, and particularly from Molière, who "by his ridicule made the enema a fashionable procedure and a matter of general conversation"; while the enema in art is exemplified by the reproduction of a painting by Jan Steen and by cartoons by Rowlandson.

The lectures on the Arts of Cupping and Leeching and Counter-irritation are of equal interest and reveal equally the scholarship of the author. Cupping and leeching and the various methods of counter-irritation described, setons, issues, the cautery, moxibustion, are all practices of great antiquity, most of which were in use till comparatively recent times. The author quotes from Sir Arthur Keith's autobiography an account of the successful cupping of a patient for acute lumbago, which he witnessed when he was a medical student, and refers to descriptions by two modern authors of their experiences and sensations on being cupped (both in France), the one for a sore throat and fever, the other for pneumonia. The reviewer recalls that when a student he found among the instruments in one of the theatre cupboards a cupping glass, a scarifier for wet cupping, and a cautery, which was called Corrigan's button, an exact replica of which is to be seen in a seventeenth-century illustration published in this volume.

So these ancient practices died hard and even to-day some, such as the art of cupping, are still practised, as the author points out, by primitive peoples. But the extent to which they were used and the number of different remedies that were applied even to one patient in one illness makes one shudder. Poor King Charles II, dying of uræmia, was subjected to bleeding, scarifying and cupping, purgation and enemata, blistering and the red hot cautery and sneezing powders, while "cephalic plasters, combined with spurge and Burgundy pitch, were applied to his feet". Poor Charles!

And so to the last essay on the Less Ancient Art of Intravenous Injection of Drugs. As the author points out Harvey's "*De Motu Cordis*" marked the beginning of intravenous medication and Sir Christopher Wren was the inventor of the method. The well-known early experiments in the transfusion of blood and later in the infusion of various and varied medicaments are graphically described by the author, who draws attention to the important milestone in the history of intravenous medication when in 1832 Thomas Latta, an Edinburgh Surgeon, recognizing that "a very great deficiency of the water and saline matter of blood" developed in cholera, and failing to compensate for the great loss of fluids by enemata of water and salt decided "to throw fluid immediately into the circulation" by the intravenous route. It is gratifying to read of the success which attended his efforts and surprising to learn of the amount of fluid which he gave—e.g. sixteen and a half pints in twelve hours and "twenty-four pints to a twenty-nine-year-old blacksmith with complete success".

The author is to be congratulated on his scholarly essays and thanked for making them available in book form, and our thanks and congratulations must also go to the publishers for their excellent production both of the typescript and the numerous illustrations.

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## Section of Anæsthetics

President—BERNARD JOHNSON, F.F.A. R.C.S.

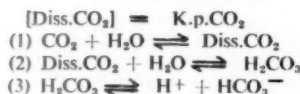
[December 3, 1954]

### Carbon Dioxide

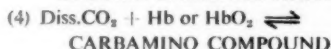
By Professor W. R. SPURRELL, M.S., F.R.C.S.

CO<sub>2</sub> is viewed as the most prominent end product of the metabolism of carbon compounds and, as such, we are accustomed to describe its distribution in the body in various combinations.

TABLE I  
CO<sub>2</sub> CARRIAGE



REACTION (2) IS ACCELERATED BY  
ENZYME CARBONIC ANHYDRASE



This gives the conventional picture of the distribution of CO<sub>2</sub> in the blood and also indicates our views as to its transport. If blood is exposed to a vacuum, 50 to 55 vol. % of CO<sub>2</sub> is released and it has come from the combinations depicted in Table I, viz. CO<sub>2</sub> in solution, H<sub>2</sub>CO<sub>3</sub>, HCO<sub>3</sub><sup>-</sup> and from combination with protein of which carb-hæmoglobin is the most important. One can extend this picture of distribution to the extravascular fluids and in this way can picture the total CO<sub>2</sub> capacity of the body which may amount to about 10 times that of the blood. In tissue fluid will be found CO<sub>2</sub> in solution, H<sub>2</sub>CO<sub>3</sub>, HCO<sub>3</sub><sup>-</sup> in about the same concentration but the protein bound CO<sub>2</sub> will be negligible. In the cells its state is not so well established but Fenn and Dubois have shown that the CO<sub>2</sub> dissociation curves for muscle, nerve and lung show similar capacities to that of blood. It would appear that the CO<sub>2</sub> capacity of tissues is of the same order as that of the blood and this would give a total body capacity of 25–30 litres. Therefore when we think of additions of CO<sub>2</sub> to or subtractions from the body we must picture that quantity in relationship to the total capacity, i.e. if we consider the production of 300 ml. of CO<sub>2</sub> in a minute by a body at rest, we must picture that 300 ml. against a background of 25 litres capacity.

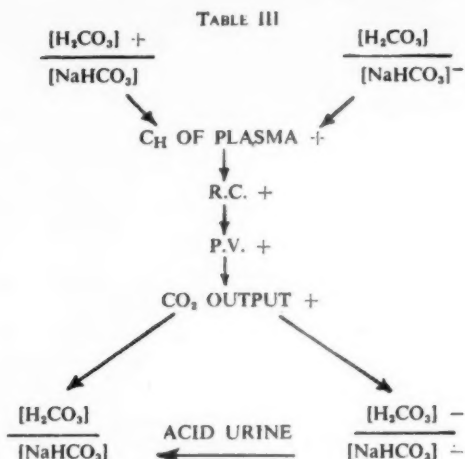
Since the carbonic acid/bicarbonate system provides one of the main buffer systems of the body, any picture of the CO<sub>2</sub> distribution in the body fluids must be closely linked with the question of the pH of the media and their buffering capacity.

TABLE II  
CO<sub>2</sub> AND H<sup>+</sup> IONS.

$$C_H = K \frac{[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3]} \quad (\text{NORMALLY } \frac{1}{20})$$

Table II shows the relationship between the C<sub>H</sub> of a solution and the relative concentrations of the carbonic acid/bicarbonate system. This simple ratio is a convenient one to bear in mind as it enables one to dissect any change in the CO<sub>2</sub> situation in terms of variations of the ratio, or of one or other of its constituents. A few reminders of such simple variations and the appropriate adjustments on the part of the organism are given in Table III.

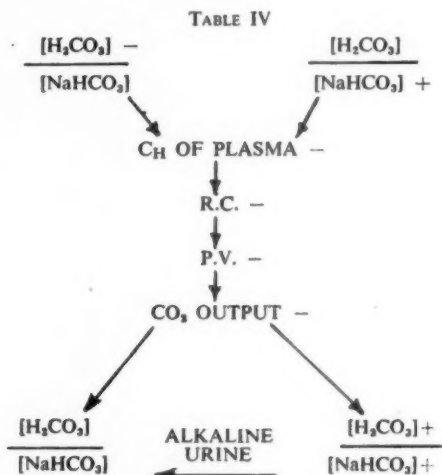
MAJ.



From a study of such variations arises the present terminology of change in acid-base balance. If a change in pH to the acid side be called a state of acidosis, it is labelled respiratory if the primary cause is a rise in the concentration of  $H_2CO_3$ , which is a simple function of the tension of  $CO_2$  in the blood: it is labelled metabolic if the primary effect is a reduction of the amount of bicarbonate due to the appearance of acid metabolites in the animal's economy (Table IV).

Similar labels are employed to the term alkalosis if the ratio is altered in the opposite direction.

The last of these fundamental points I will mention is the dynamic state of the  $CO_2$  distribution. From its site of production in the cells to its point of escape at the pulmonary



epithelium into the gas phase of the respiratory tract we believe there is a falling gradient of pressure which accounts for its steady transfer from site of production to point of escape. The capacity to maintain the  $CO_2$  content of the body within narrow limits depends upon the adjustment of these gradients to suit the rate of  $CO_2$  production. When  $CO_2$  production rises the gradient must be steepened if a corresponding increase in  $CO_2$  output is to occur; the latter *must take place* if the body is to avoid being overloaded with  $CO_2$ .

How are these gradients varied? In the tissues the tension of  $\text{CO}_2$  will be built up as a result of local increased production and so the tissue-blood gradient is steepened. In the lungs the blood-alveolar air gradient is regulated by ventilation. The breathing is so adjusted that the alveolar  $\text{CO}_2$  pressure is kept sufficiently below that of the mixed venous blood to permit of adequate diffusion of  $\text{CO}_2$  across the lung. In this sense the respiratory adequacy or otherwise of breathing is to be judged in terms of the terminal gradient it maintains across the alveolar wall. This picture of tensional gradients is important, for any manipulations of  $\text{CO}_2$  which we may make in our human subjects will lead to alterations of this gradient. The effect of any adjustment of the  $\text{CO}_2$  content of the gas breathed by a patient must be primarily assessed in terms of the alteration of gradient it imposes.

These then are the basic physiological concepts upon which I wish to build certain lessons.

(a) The large receptive capacity of body fluid, blood and tissue fluid for  $\text{CO}_2$ .

(b) The close relationship between this receptive capacity and the  $C_H$  of these fluids.

(c) The dynamic state of this receptive capacity based upon diffusion gradients.

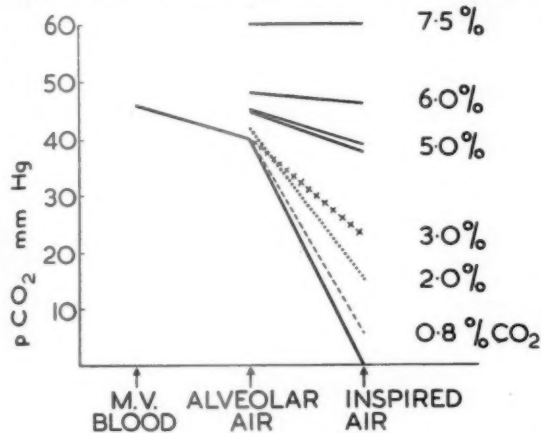


FIG. 1.— $\text{CO}_2$  gradients.

#### [ THE ADMINISTRATION OF $\text{CO}_2$

What exactly happens when we administer a respiratory mixture of gases containing  $\text{CO}_2$ ? The process is simply that of increasing the partial pressure of  $\text{CO}_2$  in the inspired air, and so altering the diffusion gradient for  $\text{CO}_2$  upon which the  $\text{CO}_2$  output of the subject previously depended.

Fig. 1 shows the effects of breathing varying mixtures of  $\text{CO}_2$  and it will be observed

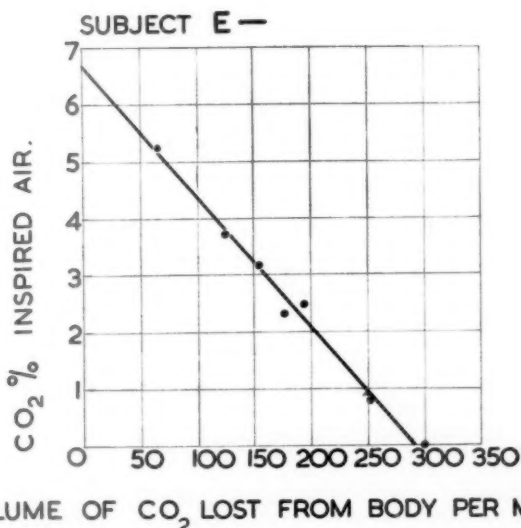


FIG. 2.—Graph relating  $\text{CO}_2$  lost from body to percentage  $\text{CO}_2$  in inspired air.  
Duration of experiment 3 minutes.

that up to 7% the effect is one of progressive diminution in the steepness of the gradient from the organism to its environment. This means an increased difficulty in the escape of  $\text{CO}_2$  and if no alteration of ventilation takes place the inevitable result must be the accumulation of  $\text{CO}_2$  in the organism with a consequent rise of  $\text{pCO}_2$  throughout. Up to 7% no  $\text{CO}_2$  enters the patient but above 7% the gradient is reversed.

Fig. 2 records the output of  $\text{CO}_2$  of a man for the first three minutes of his breathing mixtures of varying  $\text{CO}_2$  content. It shows very clearly the increasing difficulty of  $\text{CO}_2$  removal and suggests that mixtures of 7% upwards impose an absolute bar to  $\text{CO}_2$  output—in fact, at pressures above this value the slope of pressure gradient is reversed and  $\text{CO}_2$  is actually being forced into the subject and no compensation on his part is possible, i.e. the subject is facing a steadily mounting  $\text{pCO}_2$  throughout his body fluids which will soon reach a depressant or anaesthetic level. For this reason I do not propose to discuss the action of  $\text{CO}_2$  mixtures above 7%—they are essentially unreasonable and dangerous, imposing burdens upon the respiratory mechanism which it is incapable of correcting.

Up to 7%, however,  $\text{CO}_2$  mixtures are theoretically tolerable. I wish to discuss their effects in detail.

First of all it is clear that the progressive difficulty of getting rid of metabolic  $\text{CO}_2$  must mean an increasing accumulation of  $\text{CO}_2$  within the individual—it would be interesting to find out the extent of this accumulation or, as I shall call it, accretion of  $\text{CO}_2$ . In my department we have been making measurements of this quantity because we felt that it might be a useful measure of the strain that is being thrown upon the co-ordinating machinery of respiration, i.e. upon the respiratory centre. Dr. R. J. Shephard has been measuring the  $\text{CO}_2$  balance sheets of the body breathing different  $\text{CO}_2$  mixtures. This involves measurement of the  $\text{CO}_2$  content of the inspired air, the measurement of the metabolic  $\text{CO}_2$  at rest, the measurement of the  $\text{CO}_2$  cost of the increased ventilation on the income side—the  $\text{CO}_2$  of the expired air plus the  $\text{CO}_2$  accumulated in apparatus and airways on the output side—the difference between income and output being the amount accumulated by the body.

Fig. 3 gives the result of a typical experiment breathing 5%  $\text{CO}_2$  in  $\text{O}_2$ —it will be seen that up to fourteen minutes from the beginning of the experiment there is a progressive accumulation of  $\text{CO}_2$  amounting in this case to over 1,000 ml. It also shows the respiratory reaction to this accumulation which reached 15 litres per minute, i.e. a 200% increase in pulmonary ventilation. With lower  $\text{CO}_2$  mixtures the amount of accretion is correspondingly less. On the whole the findings suggest the slow approach to a steady state where, as a reaction to a certain accumulation of  $\text{CO}_2$  the ventilation has been stepped up sufficiently to restore an output of  $\text{CO}_2$  equivalent to metabolic production.

Viewed in this light an accretion of  $\text{CO}_2$  is an essential feature of the respiratory response to breathing  $\text{CO}_2$  mixtures, i.e. an additional load of  $\text{CO}_2$  must be borne. The next question we have to consider is how this load is distributed and what must be the effect of such a distribution upon the body fluids.

Clearly we must consider this load of  $\text{CO}_2$  as being distributed over the receptive capacity of the body, i.e. about 25 litres, so that we are dealing with something like a 4% increase in the body's  $\text{CO}_2$  content. But is it uniformly distributed?

If we view the process of accretion in steps, it begins by a change of gradient across the alveolar wall, a diminution in the outward diffusion of  $\text{CO}_2$ , and so the pulmonary venous blood and thus the systemic arterial blood will contain a higher concentration than before. This will diminish the gradient between capillary blood and tissues, so  $\text{CO}_2$  will accumulate

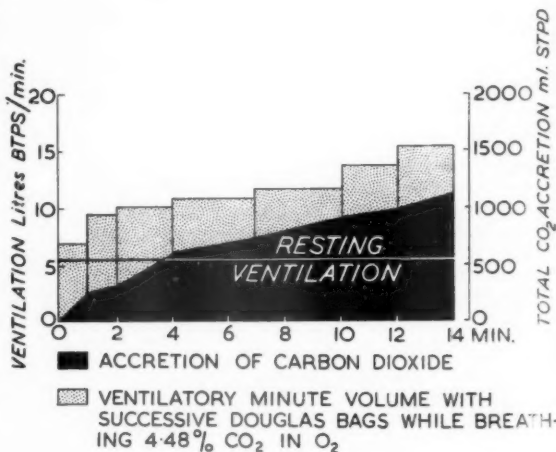


FIG. 3.

in the tissues. The whole process will be very rapid and clearly will be influenced by the rate of circulation of the blood. Shephard has made a few direct measurements of the change in  $p\text{CO}_2$  of pulmonary venous blood and aortic blood during cardiac catheterization of patients with atrial septal defects. When such patients breathed 5%  $\text{CO}_2$  mixtures a rise of 3 or 4 mm. was recorded within a minute of the commencement of inhalation and this is of the order anticipated. He made careful calculations of the amount of additional  $\text{CO}_2$  in the circulatory blood and found it about 160 ml. in the first minute falling to about half that value in the ensuing minutes. This suggests that about 10% of the  $\text{CO}_2$  accretion is accommodated in the blood and presumably the other 90% is in the extra-vascular fluids. This would mean that the litre of accumulated  $\text{CO}_2$  was proportionately shared by intra- and extra-vascular fluids, and provided the circulation was evenly distributed the  $\text{CO}_2$  distribution would be even too.

The question of the evenness of distribution must clearly be decided by the blood flow to various parts. P. Rous described a very interesting experiment in which the tissues of albino rabbits were stained by the intraperitoneal injection of phenol red so that they all carried visible indicators of their pH. The animals were then given  $\text{CO}_2$  mixtures to breathe and the colour changes were followed. The animals changed through orange to yellow and these pH changes paralleled those in the circulatory blood showing that the accretion of  $\text{CO}_2$  was of the same order of concentration in intra- and extra-vascular fluids. When these experiments were conducted under full anaesthesia patchy areas of more rapidly changing pH were often found and these always corresponded with zones of hyperaemia. So when attempting to forecast the distribution of any accumulation of  $\text{CO}_2$  due allowance must be made for any local variations in blood supply. In this respect one must remember the striking effect  $\text{CO}_2$  has in increasing cerebral blood flow so that any  $\text{CO}_2$  accumulation might be expected to affect the brain at an early stage.

What will be the effect of this accretion of  $\text{CO}_2$ ? In the case quoted an accumulation of 1 litre distributed through a body with a normal buffering capacity or  $\text{CO}_2$  capacity would lead to an increase of about 4 mm.Hg in  $p\text{CO}_2$  and a reduction in pH of about 0.02 unit. This should lead to an increase in pulmonary ventilation of about threefold and this agrees very closely with that actually observed so that these calculations appear to be reasonable. But these changes in  $p\text{CO}_2$  and in ventilation depend upon the accumulated  $\text{CO}_2$  being *evenly distributed* through a total buffering capacity of *normal value* in an individual with a respiratory centre (R.C.) of *normal sensitivity*. As both these latter quantities frequently deviate from normal so the ventilation change induced by breathing  $\text{CO}_2$  will be different. I should now like to consider some of these conditions which lead to such alterations in the ventilation response to  $\text{CO}_2$  mixtures:

- (1) Changes in the buffering capacity of the body and so in the receptive capacity for  $\text{CO}_2$  by the body fluids.
- (2) Changes in the sensitivity of the R.C.
- (3) Changes in the reactive pattern of the R.C.

TABLE V

RESPIRATORY X		METABOLIC x	
$\frac{[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3]}$	NORMAL x	$\frac{[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3] +}$	ALKALOSIS
	$\frac{[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3]}$		
$\frac{[\text{H}_2\text{CO}_3] +}{[\text{NaHCO}_3]}$		$\frac{[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3] -}$	ACIDOSIS

XXX RELATIVE EFFECTS UPON BICARBONATE  
BUFFER SYSTEM OF EQUAL ADDITION OF  $\text{CO}_2$

Here are examples of changes in the buffering capacity of the body and I have indicated by symbols the relative effect of the addition of the same amount of  $\text{CO}_2$  to each situation. The degree of pH change induced will be more or less than the normal according to the concentrations of  $\text{H}_2\text{CO}_3$  and  $\text{NaHCO}_3$ . What will be the corresponding respiratory changes?

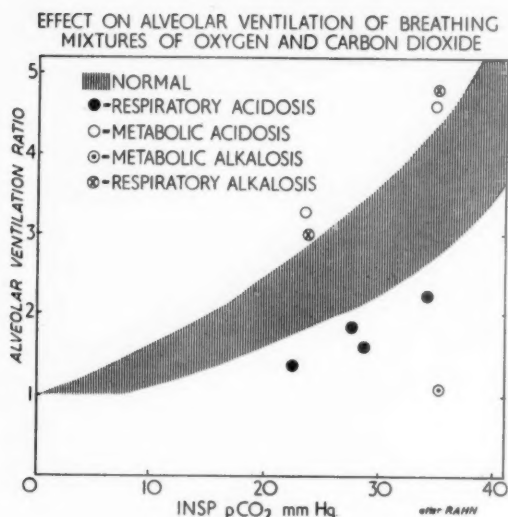


FIG. 4.

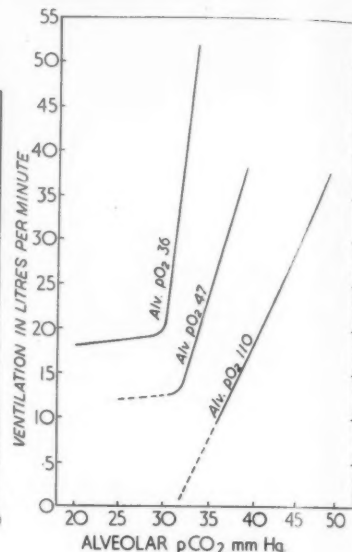


FIG. 5.

Fig. 4 shows that the respiratory response to any  $\text{CO}_2$  mixture varies in a way that corresponds to the accompanying pH change. That this response is due to the buffering capacity of tissue and not to an altered sensitivity of the R.C. is shown by the ventilation ratio returning to normal if the alkaline reserve of the blood is restored to normal value.

Thus we have a wide range of response to  $\text{CO}_2$  where the variation is due, not to any alteration of sensitivity of the R.C. but to the altered impact upon it because of variations in the buffering or  $\text{CO}_2$  receptive capacity of the body.

A good example of the second type of altered response is seen in anoxia. Present views consider that anoxia operates upon the chemo-receptors in the carotid body to produce an increase in ventilation, the so-called hypoxic drive but, in addition, the centre becomes more sensitive to  $\text{CO}_2$  and so produces a bigger response for any given increase in  $\text{CO}_2$  tension in the body.

Fig. 5 is taken from a record from Nielsen's investigation of normal subjects in whom he maintained a steady state of hypoxia at certain levels and then investigated the respiratory response to various  $\text{CO}_2$  mixtures. The graph shows two things of great importance to our subject. Firstly there is the increasing steepness of the dose/response lines with increasing hypoxia—this is the justification for stating that the sensitivity of the centre has changed because of hypoxia, for no appreciable change in buffering capacity could occur during the experimental period. The second point is that it discloses a threshold for the  $\text{CO}_2$  effect—below a  $\text{CO}_2$  tension of about 30 mm. the R.C. does not respond to  $\text{CO}_2$  drive and this threshold is almost unaffected by anoxia.

The third type of altered response to  $\text{CO}_2$  is found in conditions when the R.C. is severely disturbed by drugs or toxic agents, e.g. under morphia or in diabetic coma or in the experimental state following extreme hyperventilation against resistance. Here we have an R.C. which appears to oscillate between its responses to  $\text{CO}_2$  and hypoxia with the result that breathing is intermittent in character. In diabetic coma and after hyperventilation the intermittent breathing can be resolved by the administration of either  $\text{O}_2$  or  $\text{CO}_2$ , i.e. by the correction of either the hypoxic or the hypocapnic state.

It now remains to summarize all these points and to suggest their implication as regards the therapeutic use of  $\text{CO}_2$  mixtures.

The respiratory centre is responsible for shielding the body from excessive accumulation of  $\text{CO}_2$ . A normal healthily reacting R.C. adjusts ventilation to maintain a balance between  $\text{CO}_2$  output and  $\text{CO}_2$  production.

Breathing  $\text{CO}_2$  mixtures up to 7% diminishes the diffusion gradients and makes it more difficult to lose  $\text{CO}_2$ . An adequate or normal R.C. is capable of compensating for this

difficulty effort. A normal R.C. produces a centre for  $\text{CO}_2$  regulation of mean a 75-80 mm. 7%  $\text{CO}_2$ . Occasional with cases or chronic tension to increase such as capnia to resume  $\text{CO}_2$  to administer. Another breathing mixtures. Lastly respiratory to provide. From and the of popul with mor thrown a room. V it, to gu respirato

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difficulty by increasing ventilation but its performance is in no way improved by this extra effort. Accordingly no respiratory advantage can be claimed for administering  $\text{CO}_2$  to a normal R.C. If the R.C. is operating inadequately, i.e. failing to balance  $\text{CO}_2$  output against production, inhalation of  $\text{CO}_2$  will only add further difficulties to an already embarrassed centre for we are flogging a tired horse.

$\text{CO}_2$  mixtures above 7% reverse the diffusion gradients and force a progressive accumulation of  $\text{CO}_2$  upon the organism for which no R.C. can compensate—this accumulation will mean a rising  $\text{CO}_2$  tension in the tissues including the R.C. itself and when this reaches 75–80 mm. depression of the C.N.S. results. For this reason respiratory mixtures above 7%  $\text{CO}_2$  are unjustifiable.

Occasions when  $\text{CO}_2$  administration would appear helpful may occur when dealing with cases of long-standing respiratory acidosis such as in emphysema, chronic bronchitis or chronic laryngeal obstruction. Here the subject has lived for some time with a high  $\text{CO}_2$  tension to which presumably his R.C. has become adapted and there is a compensatory increase in buffering capacity. When such cases are subjected to ventilation with oxygen, such as may happen in "controlled respiration" by the anaesthetist, a condition of hypoxaemia may develop and in the presence of adequate oxygen the R.C. may be very slow to resume activity when the anaesthetic is over—it will require a considerable build-up of  $\text{CO}_2$  to reach an adequate threshold and this build-up may be usefully accelerated by administration of  $\text{CO}_2$ .

Another suitable situation is one to which I have already referred, viz. in the intermittent breathing following depression of the R.C. by drugs or toxic agents. Here  $\text{O}_2$  or  $\text{CO}_2$  mixtures may be effective in restoring a smooth rhythm.

Lastly  $\text{CO}_2$  inhalation can be used by the physiotherapist as a means of encouraging respiratory movement.  $\text{CO}_2$  primarily affects the depth of breathing and so can be used to provide graded breathing exercises.

From the physiological point of view sound reasons for the use of  $\text{CO}_2$  are few in number and the occasions which justify its employment comparatively rare. It has enjoyed a period of popularity as a respiratory stimulant, a bubble reputation, which is rapidly vanishing with more mature thought and experience. I should like to see all cylinders of pure  $\text{CO}_2$  thrown away and a few of 5%–7% allowed to rest in a cobwebby corner of the treatment room. We want to put more faith in the R.C., to cherish it and nourish it but not to flog it, to guard its blood supply and its oxygen supply, to regulate the pressures within the respiratory tract and then the centre will look after the  $\text{CO}_2$  problem itself.

Dr. F. F. Waddy said that in the past  $\text{CO}_2$  had been much abused in clinical anaesthesia. He mentioned the danger of allowing  $\text{CO}_2$  to accumulate in curarized patients, and asked Professor Spurrell if there was any information with regard to the effect of  $\text{CO}_2$  on other tissues, especially on the capillaries.

Dr. M. D. Nosworthy said that although he had himself written on the abuse of  $\text{CO}_2$ , he deplored Professor Spurrell's wholesale condemnation of its use. The practical anaesthetist, he said, regarded the timely addition of  $\text{CO}_2$  as a valuable *prophylactic* treatment against respiratory disturbances—for example, its early use during a nitrous oxide-oxygen-ether induction greatly reduced the likelihood of vomiting by "unprepared" obstetric patients.

Dr. R. P. Harbord asked Professor Spurrell three questions:

(1) Whether he had any evidence to show that the Henderson-Hasselbalch equation holds in patients under anaesthesia? Discrepancies between arterial and "alveolar" carbon dioxide in pathological conditions were known (Haemoglobin Committee, 1923). A recent comparison of the carbon dioxide tension for "alveolar" air and the calculated tension of carbon dioxide in arterial blood (measurements of pH and  $\text{CO}_2$  content) in patients under thiopentone anaesthesia with a muscle relaxant drug (Flaxedil), showed approximately equal values (within 5 mm.Hg), in only one-third of the examples, Harbord *et al.* (1953).

(2) How could tissue-oxygen-lack from the Bohr effect with hyperventilation during artificial respiration be recognized by the clinician in patients under anaesthesia? Haldane and Priestley (1935) had indicated the presence of tissue-oxygen-lack in the conscious subject in terms of vision and hearing, which improved by increasing oxygen tension. Was it possible to avoid the Bohr effect during anaesthesia by administering 100% oxygen?

(3) In man what was the effect on the motor end-plates of skeletal muscles of breathing excessive amounts of carbon dioxide? There was evidence from animal work in rats that the inhalation of high concentrations of carbon dioxide caused swelling of the motor end-plates.

Dr. Harbord stated that he had sampled and measured "alveolar" gases on more than 300 occasions, the majority of which were with patients breathing spontaneously to a

measured extent, and in a high proportion of these the percentage of carbon dioxide had been above seven.

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 HARBORD, R. P., PARNELL, S., and EASTWOOD, A. B. (1953) *Proc. R. Soc. Med.*, **46**, 365.

**Professor Sir Robert R. Macintosh** described experiments carried out at Madison, where research volunteers were encouraged to breathe in and out of a container to which basal oxygen was added, but in which  $\text{CO}_2$  was allowed to accumulate. All but one found it impossible to persist until unconsciousness supervened—and in this case the  $\text{CO}_2$  content of the inspired mixture was 11% v/v. R. Waters carried out, too, hyperventilation experiments on dogs, the results of which suggest that it is highly improbable that harm can materialize from overventilating a patient during operation. Professor Macintosh was surprised to hear the suggestion that  $\text{CO}_2$  might have a place in the prevention or treatment of post-operative pulmonary complications. This idea had been exploded some twenty years ago by Brock. The speaker felt strongly that  $\text{CO}_2$  had no place at all in the management of a patient in *extremis*. Carbon dioxide added to the inspired gases was a further physiological insult to which the patient succumbed all the quicker. Did Professor Spurrell agree that there was no situation in which the gravely ill patient profited by the administration of carbon dioxide?

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**Professor W. W. Mushin** (Cardiff) said that Professor Spurrell had drawn attention to an instance where the administration of a  $\text{CO}_2$  mixture might be beneficial, i.e. in a patient suffering from respiratory acidosis who did not readily resume spontaneous respiration after a period of controlled respiration. Now that they were anesthetizing an ageing population, and particularly patients who had long-standing respiratory disease, such as bronchitis and emphysema, these circumstances probably occurred more frequently than was realized. Patients such as these who did not readily start spontaneous respiration after prolonged controlled breathing might therefore need a short period of respiratory stimulation by  $\text{CO}_2$  in the shape of rebreathing, and not further vigorous ventilation with absorption of carbon dioxide as had recently been suggested. Their trouble might not be carbon dioxide poisoning, but what was to them a relative temporary depletion of carbon dioxide. In these circumstances of delayed return to breathing, he had found that a short period of ventilation with the absorber out of circuit, and perhaps an intravenous dose of nikethamide temporarily making the  $\text{CO}_2$  already in their blood an effective stimulus, would often initiate breathing. Of course cases of  $\text{CO}_2$  poisoning still occurred and were probably commoner than the reverse state. In these circumstances it was a matter of diagnosis for the anesthetist whether the delay in resuming spontaneous breathing was due to excess of  $\text{CO}_2$  in the body or to a relative depletion of this gas.

**Dr. W. N. Rollason** had seen no harm result from deliberate hyperventilation in clinical anaesthesia. He had estimated the  $\text{CO}_2$  content of the peripheral venous plasma after one and a half hours hyperventilation and had found that the  $\text{CO}_2$  content was then higher than the  $\text{CO}_2$  combining power. This was the reverse of the findings in the conscious subject at rest, and he asked Professor Spurrell if he could explain the apparent paradox.

Dr. Rollason also described changes in the ECG which were associated with a low  $\text{CO}_2$  tension. They included increased S.A. nodal activity, depressed S.T. segments and depressed T. waves, and could be corrected by administering  $\text{CO}_2$ .

**Professor Spurrell** in reply to some questions said that most people to-day would not accept in full Yandell Henderson's concept of circulatory collapse as a sequel of acapnia but would recognize that considerable instability of the circulation could develop. In that sense hyperventilation could not be considered beneficial but its effects were usually within therapeutic control.

Increased tensions of  $\text{CO}_2$  in tissues could lead to considerable dilatation of peripheral vessels. As regards other tissues plain muscle and nervous tissue were certainly susceptible.

In reply to Dr. Harbord:

**Question 1:** There was no very obvious reason why the Henderson-Hasselbalch equation should be changed by anaesthesia. Before coming to such a conclusion it would be wise to determine the carbon dioxide tensions of arterial blood by more direct means: its calculation from pH measurements of arterial blood involved many technical difficulties.

**Question 2:** The detection of this state must be an extremely difficult clinical problem since all the cardinal signs described were in conscious patients. The Bohr effect would presumably operate while using rich oxygen mixtures but could not threaten the oxygen supply to the patient.

**Question 3:** He had no knowledge on this question.

In reply to Professor Macintosh, Professor Spurrell referred the speaker to the views he had expressed on the undesirability of administering  $\text{CO}_2$  to subjects in whom the activity of the respiratory centre was inadequate.

In answer to Dr. Rollason:

The simplest explanation of this apparent paradox was that the venous sample was withdrawn from an area of stagnation in which the tissue  $\text{CO}_2$  tension was considerably above that of the alveolar air. Such peripheral stagnation was often a striking feature in hyperventilation, the subject becoming blue and cold.

[January 7, 1955]

## The Maintenance of Respiration in Respiratory Paralysis [*Abbreviated*]

By E. A. PASK, O.B.E., M.D., F.F.A. R.C.S.

*Professor of Anaesthesia, University of Durham*

ARTIFICIAL respiration has long been of interest to anaesthetists. This interest is increasing because anaesthetists are being enrolled into the teams which are being formed to deal with patients suffering from respiratory paralysis, and because artificial respiration now forms a part of many anaesthetic techniques.

Manual methods of artificial respiration for first-aid use in accidents have not, in general, been of so much interest, but anaesthetists have played a big part in a recent investigation in this field.

Let us first consider some of the changes which have occurred recently in this matter of first-aid manual artificial respiration. Until 1937, the literature in the field was very difficult to interpret. Widely varying figures for the pulmonary ventilation which could be achieved by a particular method were to be found. For example, different investigators recorded tidal volumes with the classical Schaefer's method as low as 17 ml. and as high as 1,600 ml. Probably the difficulty was that most of the subjects used for experimentation were conscious human beings who were attempting to suspend their spontaneous respiration voluntarily. Many factors other than the mechanical efficiency of the method came to play upon the results produced.

Between 1936 and 1944 two papers appeared which have always seemed to me to be landmarks in the progress in this field. One was by Professor R. M. Waters of Madison (Waters and Bennett, 1936), in which for the first time he recorded measurements of artificial ventilation upon anaesthetized unconscious patients, who could not in any way influence the results. The second paper was by Professor Hemingway and Dr. Neil of Leeds (1944) in which they measured the ventilation volumes produced by various manœuvres in dogs and drew attention very clearly to the fact that the method of artificial respiration might affect the circulation as well as pulmonary ventilation.

It seems to me that it was against the background of these two papers that wartime work on artificial respiration in this country was undertaken. As often happens in wartime, experiments had a limited and particular objective. Artificial respiration was needed in difficult and unusual conditions in which many of the accepted methods were impossible. It was necessary to discover whether the techniques which could be carried out would produce worth-while results.

Of the manual methods of artificial respiration, it might be said that there have come to be two quite different trends of thought which, at first sight, appear contrary, though on closer inspection the disparity can be reconciled. The first trend would seem to be: "It does not matter what method you use, any method will serve if the subject be alive enough and no method will work if the subject be too dead." The great anaesthetist Joseph Clover, many years ago expressed this thought. He wrote in a letter to the *Lancet*, "The method of performing artificial ventilation advocated by Dr. Howard in the *Lancet* last week, appears to be a great improvement upon other methods, more especially in the greater power it gives of compressing and expanding the lungs. But I am sure that this is not the difficult part of artificial respiration. I believe the Silvester and the Marshall Hall method, and even the intermittent compression of the chest and abdomen, would rarely fail if the air passages were free. Our experiences with gas and ether and ether and air breathed over and

over again showed a very small quantity of air to be sufficient to maintain life and to restore the respiratory movements, if they become intermittent". It is interesting that Clover does not mention the restoration of respiratory movements in patients in whom they have altogether ceased, but only in patients in whom they have become intermittent. It is interesting also that he appears to have realized quite well that the method and apparatus for anaesthesia which he advocated only allowed the patient to breathe a very small quantity of air. In later years, it was "discovered" that Clover's inhaler only permitted the patient to breathe a very small quantity of fresh air and on these grounds it was often condemned. Joseph Clover seems to have been well aware of this disadvantage and to have accepted it.

In recent times those important workers in this field, H. G. Swann and M. Brucer, have produced evidence which seems to be in conformity with Joseph Clover's view. Amongst their many papers, one in the *Journal of Applied Physiology* makes this point rather clearly (Brucer and Swann, 1951). In these experiments, dogs were subjected to the inhalation of pure nitrogen. Respiration became irregular and finally stopped. At this point the animal's blood pressure was reasonably high and it so continued for a minute or two after respiration had ceased. Then the blood pressure began to fall very steeply so that on the average the systolic pressure fell from 110 to 70 mm.Hg in the space of 17 seconds. If artificial respiration was applied to the apnoeic animals at a time when the blood pressure was still above 100, almost any method was successful in reviving a large proportion of the animals. If the application of artificial respiration was delayed until the blood pressure had fallen below 70 systolic, an event which occurred on the average some 17 seconds later, then no available method was successful in reviving them.

Some of the methods of revival which succeeded, provided that the blood pressure was greater than 100 systolic, were the following:

- (a) A single inflation of the lungs with pure oxygen.
- (b) A periodic inflation of the lungs with a mixture of 2% oxygen in nitrogen.
- (c) A periodic inflation of the lungs with air using such small tidal volumes that the animal's dead space was only just exceeded.

Once the animals' systolic pressure had fallen below 70, even the periodic inflation of the lungs with oxygen failed to revive them. Thus, in fulminating anoxia of this kind, it is the state of the subject much more than the nature of the method of artificial respiration, upon which the outcome depends. Swann and Brucer carefully stress that their results apply only to this kind of fulminating anoxia, such as might occur in drowning. But there are other circumstances when artificial respiration may be needed in which the conditions are quite different.

When a patient is poisoned with a narcotic, for example a barbiturate, respiration may be profoundly depressed and irregular. If nothing can be done, or if the assistance to respiration be inadequate, then a biochemical disturbance will develop and become progressively worse so that eventually the patient may die. In these cases, assistance to the respiratory mechanism may be necessary over a very long time and it is important that such assistance should be capable of producing adequate pulmonary ventilation, for it cannot be expected that the patient's own breathing mechanism will quickly take over the task. It is possible that poisoning with the anti-cholinesterase substances might lead to a situation of this sort and that poisoning from these substances might occur on a fairly wide scale in a future war.

It is from the consideration of this sort of situation that the contrary trend of thought has arisen whereby investigators are now seeking the method of manual artificial respiration which will produce the greatest possible pulmonary ventilation. An extensive programme of investigation into manual methods of artificial ventilation has recently been carried out in the United States with the purpose of discovering the one best able to produce the maximum pulmonary ventilation. The work was carried out at five Universities and is reported in the *Journal of Applied Physiology* (1951). A variety of methods was studied and the pulmonary ventilation was recorded. In addition, the effects upon the circulation, the ease with which the methods could be carried out by the operators, and also taught to new operators, were investigated. The subjects were all unconscious, apnoeic, healthy human beings who had been anesthetized with thiopentone and given a relaxant.

It is extremely difficult and, indeed, dangerous to attempt to summarize in a few words such a large and important piece of work. The conclusion reached was, however, that the method of Schaefer, hitherto generally accepted, was a good deal less effective than an alternative method—the Holger-Nielsen—and that the latter should replace Schaefer's method for general use. It was also concluded that the Holger-Nielsen method was sufficiently easy to perform and to teach.

It is natural, therefore, that one should be particularly interested in the comparative

results of these two methods, the one which is to be displaced, and the other which it is recommended should supplant it. Schaefer's method is, of course, a prone/pressure method in which the operator causes active expiration by pressure upon the rib cage and inspiration occurs by the elastic recoil of this same structure. In the Holger-Nielsen method the subject is also prone, expiration is produced again by pressure upon the rib cage but there is an active inspiratory movement produced by drawing the subject's elbows upward and slightly away from the ground.

It has to be remembered that the cycle of events in the Schaefer technique is shorter than that of the Holger-Nielsen method, so that whereas with the Holger-Nielsen method only twelve respiratory movements a minute can usually be achieved, with Schaefer's method twenty or twenty-two may be possible. When this difference is taken into account, the results suggest that Schaefer's method can usually produce a minute volume which is just about adequate for the maintenance of life, but the Holger-Nielsen method is capable of producing considerably greater minute volumes, of the order of 10-12 litres per minute. There was, however, a more serious reflection upon the efficiency of Schaefer's method. It was suggested that even though an apparently sufficient minute volume might be produced by this technique, the oxygen saturation of the blood might, nevertheless, be extremely low. The explanation proffered is that Schaefer's method produces not only small ventilation of the lungs, but also uneven ventilation, and in certain of the patients the oxygen saturation of the blood fell as low as 40%, even though the minute volume was not grossly inadequate. The detailed data is sometimes difficult to reconcile, but this suggestion that Schaefer's method produces uneven ventilation of the lungs is a very serious one. It has probably been accepted for some years that Schaefer's method could not do more than produce barely adequate ventilation, but that the ventilation is imperfect in nature as well as in quantity is a new and serious suggestion. This critical point might be tested by asking a simple question: Can Schaefer's method maintain oxygen saturation when the subject breathes air alone? Some of us are attempting to test this point.

From a practical point of view, Schaefer's method has some advantages over the Holger-Nielsen, if it could be shown to be sufficiently effective for most circumstances. It is a little easier to perform. Again, the operator in Schaefer's method kneels beside the patient's trunk and if a second person be present he can gain free access to the head in order to make sure that the air passages are clear. With the Holger-Nielsen method the operator must kneel at the patient's head and it is difficult for a second person to maintain a clear airway, for he cannot readily gain access to the subject's head.

If one reflects upon Joseph Clover's stress upon the importance of the air passages being free, a point which is undoubtedly correct, and if one reflects upon the fact that in certain acute asphyxial emergencies recovery does not seem to depend upon the production of large pulmonary exchange, then one is bound to wonder whether Schaefer's method has not been rather too lightly displaced from general use, though there is no doubt that in some emergency situations a method is required which will produce the maximum possible pulmonary ventilation and there is also no doubt that the Holger-Nielsen method will do this better than Schaefer's.

Let us now turn our attention to some of the developments that have occurred in recent years in mechanical methods of artificial respiration. The situation is very confusing because so many new devices and machines have appeared. A good many of them have been reviewed by Professor Mushin and Dr. Rendell-Baker in the *British Journal of Anæsthesia* (1954). Their review was more concerned with mechanisms of the machines than with their function. It may be profitable to try to work out some sort of scheme in which the various new methods are classified according to their function.

(1) *Electrophrenic respiration*.—This is an old technique but the revival and production of the modern electrophrenic stimulator is associated with the names of Dr. S. J. Sarnoff and Dr. K. W. Cross. A rhythmic electrical stimulus is applied to the phrenic nerve, causing contraction of the diaphragm. The method is "physiological" but it can only work if the phrenic nerve and the neuromuscular junction are intact. It is not therefore normally useful in cases of poliomyelitis nor for patients who have received a relaxant. Difficulties arise when prolonged artificial respiration is needed, for if the stimulus is applied percutaneously it is generally necessary to maintain the electrode in position by hand, since clamps or holders are not sufficiently versatile to deal with a living patient's movements. Implanted electrodes have been tried but do not yet seem to be generally acceptable.

(2) *Electromuscular respiration*.—The idea behind this technique seems to be that the stimulus should be applied to the motor points of as many respiratory muscles as possible, but, unfortunately, the motor points of the diaphragm are not really accessible to stimulation and those of the intercostal muscles are, of course, multiple. The method is somewhat cumbersome and probably is not effective in producing complete artificial maintenance of

respiration. It may have some place in the education of patients who are recovering from respiratory paralysis.

(3) *Eve's method*.—Eve's method can be done manually as well as by means of some mechanism such as a rocking stretcher or a rocking bed. It is not new, but the use of rocking beds has recently been shown by Schuster and Fischer-Williams (1953) and others to be helpful to those patients recovering from poliomyelitis who can breathe when awake by the use of accessory respiratory muscles, but who cannot maintain adequate respiration when asleep. No doubt they gain some physical assistance from the rocking bed but it seems also possible that the rocking acts as a conditioned stimulus leading them, perhaps, to make use of accessory muscles even though asleep.

(4) *Cabinet respirators*.—It is now recognized that when a cabinet respirator is operated only with intermittent negative pressure within the cabinet, the effect upon venous return to the heart is similar to that produced by intermittent positive pressure respiration, since the pressure within the thorax will tend to be positive in relation to that around the body as a whole. If a positive pressure expiratory phase be introduced as well as the negative pressure inspiratory phase, venous return to the heart is somewhat assisted.

Many modifications to the design of cabinet respirators have emerged in recent years. Some of these seem unnecessary, indeed even embarrassing, to the practical operator. Some of the advances are worth while and these include: (a) Means of increasing the ease and the speed of opening the respirator so that nursing attention can readily be given and so that the patient's position can be changed.

(b) Alterations to the head-end of the respirator and to the head-rest so that it is possible to nurse the patient in a prone position with a head-down tilt and thus facilitate the drainage of secretions from the pharynx and respiratory tract.

(c) Improvements in the comfort of the fitting of the airtight collar around the patient's neck together with the possibility of using a cabinet respirator for a patient who has a tracheotomy opening.

(5) *Cuirass respirators*.—Considerable improvements in the design of cuirass respirators have been introduced by J. T. Scales and others (1953), particularly in the development of individually mouldable cuirasses and in alteration in the shape of the cuirass so that pulmonary ventilation is improved. It is very much to be hoped that further development will occur in this field for the cuirass respirator must surely embarrass the circulation less than nearly all other types. If it can be made comfortable enough for continuous use over long periods, if it can be made capable of producing really adequate ventilation in all patients, and if it can be so modified that it be possible to nurse the patient in the prone position, then surely the future for this type of respirator must be very important.

(6) *Intermittent positive pressure and intermittent positive/negative pressure respirators*.—A multitude of these devices have appeared recently, following upon the epidemic of poliomyelitis which occurred in Denmark. These respirators can be used for short periods with a mask or mouthpiece, but if they are to be used for long periods, then a tracheotomy fitted with a tube which has an airtight seal against the trachea wall is necessary. In appropriate cases, there are incidental advantages in the tracheotomy in that it allows the ready removal of secretions from the respiratory tract and effectively prevents the risk of entry of food and saliva into the lungs. This type of respirator is extensively used during anaesthesia.

When an intermittent positive pressure respirator is used, the mean intrathoracic pressure is necessarily greater than it is when the patient is breathing spontaneously. A good deal of discussion has therefore centred around the possible importance of maintaining a low mean intrathoracic pressure. At first sight, this appears very important since the heart is not a suction pump and the filling of the right auricle, which lies within the thorax, depends upon the difference in pressure within the great veins just outside the thorax, and the pressure in the right auricle. However, patients possess physiological compensatory mechanisms and if the pressure in the right auricle be raised artificially, then pressure in the great veins outside the thorax may also be raised so that auricular filling in diastole is maintained. There seems little doubt that a fit patient can make this compensation quite adequately and even though the mean intrathoracic pressure be rather high, no serious adverse consequences will follow.

In 1943 Beecher *et al.* showed that healthy dogs could withstand rather high mean intrathoracic pressures quite well, but that when they had been bled, the effect of this pressure upon the circulation became critical.

Now, Maloney *et al.* (1953) have elegantly demonstrated that healthy patients can compensate for an increase in mean intrathoracic pressure, but, equally certainly, that patients in whom the circulation is precarious cannot do so. If we then ask the question, "Must

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we concern ourselves seriously to secure the lowest possible mean intrathoracic pressure?", the answer seems to be—

(a) We need not, if the respirator is required only for short periods as, for example, when it is used to permit a cabinet respirator to be opened for nursing care.

(b) We need not, when the respirator is to be used during anaesthesia for thoracic surgery, with open chest.

(c) We need not, when the respirator is to be used only upon patients whose circulation is vigorous.

(d) We must concern ourselves with this factor when the patient's circulation is precarious. It is believed that this factor contributed significantly to circulatory failure in some of the patients in the poliomyelitis epidemic in Denmark.

When considering whether a particular machine is suitable for our purpose, it seems reasonable to ask the following questions:

(1) *Can correct pulmonary ventilation be secured?* Many machines are pressure controlled—that is, the patient's lungs are inflated until a "cut-off" pressure is reached when the cycle reverses. It is sometimes difficult to secure sufficiently low cut-off pressure. The usual range is 5 cm.  $H_2O$ –30 cm.  $H_2O$ . A few machines are volume controlled and inject a predetermined volume of air, regardless of pressure, though there are usually safety devices.

(2) *Can a low mean intrathoracic pressure be secured?* An intermittent positive pressure machine should be capable of rapid inflation at 40/80 litres/min. so that adequate distension of the lungs can quickly be made and therefore the positive pressure phase can be very short. "Cut-off" must be immediate and there must be no residual positive pressure in the system during exhalation. The rapid inspiration must be possible even if the repetition rate is slowed down.

If a negative (suction) phase be possible during exhalation, the mean intrathoracic pressure can be lower still.

(3) *If the patient is making inadequate attempts to breathe, can the machine "match" them?* The repetition rate of the machine must be sensitively and continuously controllable and should not change only by "steps". When this is so, any regular rhythm can be matched, but if the patient's attempts are irregular, then only a "patient-triggered" respirator will "match" his efforts. These devices inflate the patient's lungs whenever an attempt at inspiration is made. They may also have a basic rhythm.

(4) *With what are the lungs inflated?* This may be atmospheric air, or air at high or low pressure may be needed. It is important to know:

(a) Whether enrichment with oxygen is feasible.

(b) Whether humidification is feasible.

(c) Whether anaesthetic gases can be used and if so,

(d) Whether a closed circuit or a semi-closed one can be used.

(5) *What provides the energy to operate the mechanics of the respirator?* If this be electric, then the device must be free from explosion risks if it is to be used in the operating theatre. Many machines derive their energy from the respired gases. Some of these can be described as "economical" in that only a small amount of gas is used to operate the mechanism and they can sometimes be operated by the gases flowing from an anaesthetic machine. Other machines are "wasteful" of gases but this is of no critical significance if they are to be fed by air at low pressure from a blower, for then there is usually an abundant supply.

A few machines use suction as their motive force.

(6) *Is the mechanism likely to be reliable and easy to repair?* A word of caution is that apparent simplicity is not always helpful. A complicated-looking machine may have a separate mechanism for each function and may therefore be easier to understand and adjust than a machine in which a single mechanism performs several functions.

This catalogue of the characteristics of intermittent positive pressure machines is long and tedious, but an understanding of them is important for it is all too easy to acquire an excellent machine which has features which make it very inconvenient for a particular application.

Intermittent positive pressure respirators are not new. The first devices were little more than mechanically operated bellows. These were simple and reliable, but they were not versatile and they paid little regard to physiological consideration. A variety of "spiropulsators" and "pneumoflators" soon appeared which were much more versatile but bought the advantage at the expense of considerable complexity of mechanism. The poliomyelitis outbreak in Denmark turned designers' minds not only to simpler designs but to designs which could quickly be made up in emergencies. Claus Bang (1953) led this

trend. As the urgency decreased after this outbreak, the need for additional facilities became evident. Rapid inflation, sensitive rate control, "patient-triggering", and negative pressure phases were added, and the trend to simplicity was reversed.

Now, it seems to me, the requirements for such a machine are beginning to become stable in our minds and it is possible for designers to turn their thoughts again to simplifying the operating mechanism itself. This welcome trend to simplicity is already becoming evident.

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**Dr. J. M. K. Spalding** (Oxford) described some recent work done in the Respiration Unit at Oxford in association with Dr. Ritchie Russell and Dr. Crampton Smith. He produced evidence that in paralysed patients tidal air is practically proportional to inspiratory pressure, and that the rate of flow of air is highest at the beginning of inspiration and falls off rapidly thereafter. An adequate tidal air may be obtained with inspiration lasting only 0.6 second, and there is little object in prolonging it more than 1.5 seconds. Evidence was produced that the rate of rise of pressure during inspiration was important, and that a rapid rise was advantageous. When it is necessary to increase a patient's ventilation, it is more satisfactory to increase the tidal air than the respiratory rate. (Dr. Spalding's communication will be published in full elsewhere.)

**Dr. W. Ritchie Russell** (Oxford) said that from the experience of his Unit, patients could be kept in good condition on intermittent positive pressure respiration through a cuffed tracheotomy tube for periods of several months, without any negative phase being used during expiration.

**Dr. A. B. Kinnier Wilson** said that there were many types and shapes of cuirass respirator, of which the best was the chest-abdomen type. This was able to act on the diaphragm and so ventilated the lung bases better than the shorter chest type which merely pulled the sternum forward. With cuirasses of the former type he had achieved tidal volumes of over a litre, as compared with the average maximum of only 500 ml. with the chest type.

**Dr. John Gillies** spoke of his interest in rotary air-compressors for activating respirators used in cases of poliomyelitis. Complete elimination of fine oil smoke had been a problem and in view of the possible ill-effects on the lungs of even minute quantities of such smoke over a long period he sought the opinion of Professor Pask on the most effective method of filtration.

**Dr. J. G. Bourne** asked whether, when simple positive pressure artificial respiration was being administered by rhythmical compression of a breathing bag, tilting the patient a little bit head down would not substitute a small hydrostatic pressure sufficient to compensate for loss of the thoracic pump and ensure an adequate venous return to the heart. If this were so there would be no need to introduce into artificial respiration a negative pressure phase.

In reply to the discussion, **Professor Pask** said that he thought it would be reasonable to combat the effects of positive pressure within the thorax by posture, but that in extreme circulatory collapse the benefit to be gained from this might be small. The risk of inhalation of mineral oil vapour due to certain types of blower had to be considered, but the use of suitable filters and especially some form of humidifier should minimize this risk.

The difficulty of considering the respirator, connecting piping, respiratory tract and patient's lungs as a single viscous-elastic system, was considerable. It must be recognized that measurement of the relation between pressure and rate of flow, or time of filling of the lungs, at one point in the system did not necessarily reflect a characteristic of the patient, but might be determined by the characteristics of the respirator in combination with the patient.

The figures obtained with a respirator of one type might be different from those obtained with a respirator of another type, unless pressure changes were measured deep in the patient's trachea.